QUERCETIN

This substance was considered by previous working groups, in 1982 (IARC, 1983) and 1987 (IARC, 1987). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 117-39-5

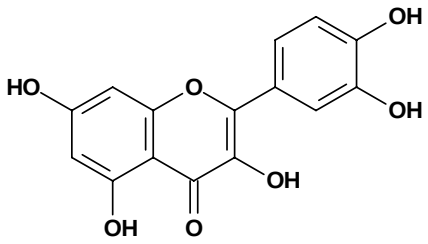
Deleted CAS Reg. No.: 73123-10-1; 74893-81-5

Chem. Abstr. Name: 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-1-benzopyran-4-one

IUPAC Systematic Name: 3,3′,4′,5,7-Pentahydroxyflavone

Synonyms: CI 75670; CI Natural Yellow 10; 3,3′,4′,5,7-pentahydroxyflavone; 3,4′,5,5′,7-pentahydroxyflavone; 3,5,7,3′,4′-pentahydroxyflavone; quercetine

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_{15}H_{10}O_7$ Relative molecular mass: 302.24

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Pale-yellow needles (dihydrate) (Budavari, 1996)

(*b*) *Boiling-point*: Sublimes (Lide, 1997)

(*c*) *Melting-point*: 316.5°C (Lide, 1997)

(*d*) *Solubility*: Slightly soluble in water and diethyl ether; soluble in ethanol and acetone (Lide, 1997)

(*e*) *Conversion factor*: $mg/m^3 = 12.36 \times ppm$

1.2 Production and use

Information available in 1995 indicated that quercetin was produced in Brazil, Germany, Japan, Spain, Switzerland, the United Kingdom and the United States (Chemical Information Services, 1995).

Quercetin has been used in medicine to decrease capillary fragility. It has also been used in dyes and as a veterinary drug (National Toxicology Program, 1991).

1.3 Occurrence

Quercetin is widely distributed, usually as a glycoside, especially in the peels and leaves of many fruits and vegetables (Budavari, 1996). No data were available on occupational exposure to or the environmental occurrence of quercetin.

1.4 Regulations and guidelines

No international guidelines for quercetin in drinking-water have been established (WHO, 1993).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Previous evaluation

Quercetin was tested for carcinogenicity in three experiments in rats, two in mice and one in hamsters by oral administration. Negative results were obtained in all but one of the studies in rats; intestinal and bladder tumours were produced in the one study with positive results. Quercetin was also tested by skin application in one study in mice, with a negative outcome for skin tumours. In one study in mice that received implantations of cholesterol pellets in the bladder, bladder carcinomas were produced in both treated and control groups. Rutin, the 3-rhamno-glucoside of quercetin, was tested by oral administration in one study in rats and one study in hamsters. No significant difference in tumour incidence from that in controls was observed (IARC, 1983).

New studies

3.1 Oral administration

Rat: Groups of 15 male and 15 female Fischer 344 rats, six weeks of age, were given quercetin (purity, 99%) in the diet at a concentration of 0.1% for 540 days. All of the treated animals survived. The incidence of tumours in the treated groups was not statistically different from that in controls (Takanashi *et al*., 1983). [The Working Group noted the small numbers of animals, which made the study inadequate for evaluation.]

Groups of 50 male and 50 female Fischer 344/DuCrj rats, six weeks of age, were fed quercetin (purity, at least 99.4%) in the diet at concentrations of 0 (control), 1.25 or 5% for 104 weeks and were maintained for a further eight weeks without quercetin. The high dose was the maximum tolerated. At the end of the 112-week study, the survival rates for males were 56, 66 and 68% and those for females were 66, 62 and 72% for the three groups, respectively. No statistically significant increase in incidence of tumours was seen, but males at the high dose showed a significant increase in the incidence of non-neoplastic hyperplastic polyps of the caecum, and one adenoma and two adenocarcinomas of the caecum were found in males at this dose and two adenomas of the colon occurred in females (Ito *et al*., 1989).

Groups of 70 male and 70 female Fischer 344/N rats, seven weeks of age, were given quercetin (purity, > 95%; ellagic acid was the predominant impurity at 1.1–2.6%) in the diet at concentrations of 0, 1000, 10 000 or 40 000 mg/kg (ppm) for 104 weeks. Ten animals per group were killed at 6 and 15 months. The high dose approached the maximum tolerated. Treatment did not affect the survival of either male or female rats, but the decreased body-weight gain of animals at the high dose was attributed to quercetin. As shown in Table 1, males at the high-dose had an increased incidence of renal tubular tumours (three adenomas and one adenocarcinoma) with none in control males, but the increase did not achieve statistical significance. After step-sectioning, a total of nine renal tubular tumours were found in these animals, and the increase was statistically significant. The severity of spontaneous progressive nephropathy was exacerbated in male rats by exposure to quercetin (Dunnick & Hailey, 1992; National Toxicology Program, 1992).

Table 1. Incidences of primary renal tubular adenomas or carcinomas in Fischer 344 rats exposed to quercetin

Treatment (ppm)	Animals with tumours			
	Males		Females	
	Initial evaluation	Single plus step-section	Initial evaluation	Single plus step section
Control	0/50	1/50	0/49	1/49
1 000	0/50	2/50	0/49	–
10 000	0/50	7/50[a]	1/50	–
40 000	4/50[b]	9/50[c]	0/50	0/50

From National Toxicology Program (1992)
–, not determined
[a] $p < 0.0032$
[b] $p = 0.064$
[c] $p = 0.01$

3.2 Administration with known carcinogens

Many new studies have been conducted in which quercetin was tested in various initiation–promotion regimens with various carcinogens, with variable results. Both enhancing and inhibiting activity were found.

Mouse: In a study of skin carcinogenesis in groups of 30 CD-1 mice, prior treatment with quercetin had no effect on initiation of tumours by benzo[*a*]pyrene (Chang *et al*., 1985). Quercetin given by intramuscular injection or in the diet was reported to enhance the carcinogenicity of 3-methylcholanthrene in C57BL/6 mice by significantly shortening the latency of sarcomas at the site of intramuscular injection of 3-methylcholanthrene (Ishikawa *et al*., 1985). When quercetin was tested as a potential initiator in a two-stage model of mouse skin carcinogenesis with 12-*O*-tetradecanoylphorbol 13-acetate (TPA) as the promoting agent, local application twice a week for five weeks induced two skin tumours in 1/21 mice after 47 weeks of TPA treatment. No skin tumour was produced with quercetin alone or with dimethyl sulfoxide plus TPA (Sato *et al*., 1987).

Dietary administration of quercetin has been shown in some studies to inhibit tumours, including azoxymethane-induced colonic tumours in mice (Deschner *et al*., 1991) and skin tumour formation in three models of skin carcinogenesis in mice when administered by topical application (Nishino *et al*., 1984; Khan *et al*., 1988, Mukhtar *et al*., 1988).

Rat: In a model of pancreatic carcinogenesis with *N*-methyl-*N*-nitrosourea as the carcinogen, quercetin significantly enhanced focal acinar-cell hyperplasia in rats of each sex and produced a non-significant increase in the incidence of carcinomas *in situ* (Barotto *et al*., 1998).

Quercetin did not enhance the bladder tumour incidence induced in rats by *N*-nitrosobutyl-*N*-(4-hydroxybutyl)amine (Fukushima *et al*., 1983; Hirose *et al*., 1983), mammary gland, ear-duct and forestomach tumours induced in rats by 7,12-dimethylbenz[*a*]anthracene (DMBA) (Hirose *et al*., 1988) or intestinal carcinogenesis induced in rats by methylazoxymethanol acetate (Kato *et al*., 1984). In models of colon and mammary carcinogenesis, quercetin inhibited the development of aberrant crypt foci in rat colon (Matsukawa *et al*., 1997) and the incidence of DMBA- and *N*-methyl-*N*-nitrosourea-induced mammary cancer (Verma *et al*., 1988).

Hamster: Administration of 3% quercetin in the diet of male Syrian hamsters increased the mean number of renal tumour masses and the incidence of metastases after subcutaneous implants of oestradiol (Zhu & Liehr, 1994). Quercetin inhibited DMBA-induced buccal pouch carcinogenesis in hamsters (Balasubramanian & Govindasamy, 1996).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

After oral administration of a single dose of 4 g quercetin to four male and two female volunteers, neither quercetin nor its conjugates was detected in the blood or urine during the first 24 h; 53% of the dose was recovered in the faeces within 72 h. After a single intravenous injection of 100 mg quercetin to six volunteers, the blood plasma levels declined biphasically, with half-lives of 8.8 min and 2.4 h; protein binding exceeded 98%. In the urine, 0.65% of the intravenous dose was excreted as unchanged quercetin and 7.4% as a conjugate within 9 h; no further excretion occurred up to 24 h (Gugler *et al.*, 1975).

One male and one female volunteer were given a diet containing quercetin glucosides (64.2 mg expressed as the aglycone). The mean peak plasma concentration of quercetin was 196 ng/mL which was reached 2.9 h after ingestion. The time-course of the plasma concentration of quercetin was biphasic, with half-lives of 3.8 h for the distribution phase and 16.8 h for the elimination phase. Quercetin was still present in plasma 48 h after ingestion (Hollman *et al.*, 1996). Similar findings were made for nine other human subjects (Hollman *et al.*, 1997). The authors suggested that this slow elimination rate would lead to accumulation in plasma with repeated ingestion.

The metabolites of quercetin flavonols identified in urine samples collected from two male volunteers who consumed their habitual diets for three days were 3,4-dihydroxyphenylacetic acid, *meta*-hydroxyphenylacetic acid, and 4-hydroxy-3-methoxyphenylacetic acid (Gross *et al.*, 1996).

4.1.2 *Experimental systems*

Autoradiographic analysis of a fasted rat 3 h after administration of a single oral dose of 2.3 mg/kg bw [4-^{14}C]quercetin showed that although most of the radiolabel remained in the digestive tract it also occurred in blood, liver, kidney, lung and ribs. After oral administration of 630 mg/kg bw of the labelled compound to rats, 34% of the radiolabel excreted within 24 h, expressed as a proportion of the dose, was expired carbon dioxide, 12% in bile and 9% in urine; within 48 h, 45% was recovered in the faeces. Approximately 60% of the radiolabel in the faeces was identified as unmetabolized quercetin. Sulfate and glucuronide conjugates of quercetin and of an unidentified flavonoid were found in bile and urine. Incubation of [4-^{14}C]quercetin with rat caecal and colon contents *in vitro* under conditions that were probably anaerobic resulted in the release of 6% of the radiolabel as carbon dioxide (Ueno *et al*., 1983).

After oral administration of 0.5 g/kg bw quercetin to rabbits, the main urinary metabolites were 3,4-dihydroxyphenylacetic acid, 3-methoxy-4-hydroxyphenylacetic acid and 3-hydroxyphenylacetic acid (Booth *et al*., 1956).

Quercetin was rapidly metabolized by *O*-methylation in male Syrian hamsters (Harlan Sprague-Dawley) two to four months of age given an intraperitoneal injection of 50 or 500 mg/kg bw quercetin mixed in 50% glycerol:water. The major metabolite of quercetin in the ether extract of urine was identified as 3′-*O*-methylquercetin. A major portion of the 3′-*O*-methylquercetin eliminated in urine was conjugated by glucuronidation or sulfation. Only 2% of the total flavonoid content of the extract was unmetabolized quercetin. The rates of *O*-methylation of quercetin *in vitro* catalysed by porcine liver catechol-*O*-methyltransferase or cytosolic fractions of Syrian hamster kidney were about three orders of magnitude higher than the rates for endogenous catechols, such as catechol oestrogens and catecholamines (Zhu *et al*., 1994).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

The acute oral and subcutaneous LD_{50} values of quercetin in the mouse are 160 and 100 mg/kg bw (Sullivan *et al*., 1951). Rabbits were unaffected by intravenous administration of 100 mg/kg bw or by diets containing 1% quercetin for 410 days (Ambrose *et al*., 1952).

Male and female Fischer 344 rats were given a diet containing 0, 1.25 or 5% quercetin for 104 weeks and then a normal diet for a further eight weeks (see section 3 for details), with average intakes for males and females, respectively, of 427 and 497 mg/kg bw per day for those consuming the 1.25% quercetin diet and 1926 and 2372 mg/kg bw per day for rats consuming the 5% diet. With 5% quercetin, the body weights of males and females at the high dose were decreased throughout the study. There were no treatment-ascribed effects on clinical signs, deaths or the results of urinalysis or haematology. Decreases in serum glucose concentration and increases in some relative organ weights were observed at the high dose, the latter being attributed to growth retardation. A higher incidence of hyperplastic polyps of the caecum was observed at the high dose in comparison with controls. No significant increase in adverse changes was observed in other organs (Ito *et al*., 1989).

Male and female Fischer 344 rats, seven weeks of age, were given quercetin in the diet at concentrations of 0, 1000, 10 000 or 40 000 mg/kg of diet (ppm) for two years (to provide estimated doses of approximately 40, 410 and 1900 mg/kg bw per day during the second year). Rats were necropsied after 6 and 15 months of treatment for interim evaluations. The body weights of animals at the high dose were reduced relative to those of controls during the last year of the study. The only treatment-related toxic lesions were detected microscopically at the 6- and 15-month evaluations and consisted of pigmentation of the superficial epithelium of the glandular stomach and the distal segments of the small intestine, the latter also being seen at two years. The authors noted that quercetin is a yellow compound, and adsorption of this chemical or a metabolite was probably the cause of the tissue

pigmentation. After two years of quercetin administration, the incidence of hyperplasia of the renal tubular epithelium was increased, with mild exacerbation of chronic nephropathy in male rats (see section 3 for neoplastic effects). Male rats also had dose-related increases in the incidence of renal pelvic epithelial hyperplasia and of parathyroid gland hyperplasia, which are commonly observed in male rats with advanced nephropathy (Dunnick & Hailey, 1992).

Quercetin inhibits Na^+-K^+ ATPase in both plasma and mitochondrial membranes (Lang & Racker, 1974; Suolinna *et al*., 1975). Inhibition of glucose oxidation in neutrophils via the hexose monophosphate pathway and inhibition of uptake of 2-deoxyglucose were also reported (Long *et al*., 1981). Quercetin inhibited glycolysis in Erhlich ascites tumour cells, due probably to a lowering of the intracellular pH by inhibition of lactate efflux (Belt *et al*., 1979). Administration of 5–20 μg/mL quercetin caused pronounced inhibition of the growth of several cell lines (Suolinna *et al*., 1975). Liposome-encapsulated quercetin inhibited DNA synthesis in Ehrlich ascites tumour cells (Podhajcer *et al*., 1980).

Quercetin inhibited ethoxyresofurin *O*-deethylation by liver microsomes prepared from β-naphthoflavone-treated Long Evans rats, by 15% at a concentration of 10 nmol/L to 80% at 250 nmol/L (Sousa & Marletta, 1985); and it had a similar effect in microsomes prepared from 3-methylcholanthrene-treated Sprague-Dawley rats, causing 50% inhibition at a concentration of 15 μmol/L (Moon *et al*., 1998). Quercetin also inhibited ethoxyresorufin *O*-deethylase activity in human microsomes, causing 50% inhibition at 12 ± 6 μmol/L (Siess *et al*., 1995). Quercetin also inhibited *para*-nitroanisole demethylation and benzo[*a*]pyrene hydroxylation reactions of β-naphthoflavone-treated Long Evans rat microsomes, by 26% at a concentration of 0.25 μmol/L, 78% at 5 μmol/L, 32% at 0.1 μmol/L and 95% at 500 μmol/L (Sousa & Marletta, 1985). Hydroxylation of benzo[*a*]pyrene by a sample of human liver microsomes was also inhibited by quercetin, by 14% at a concentration of 0.005 mmol/L and 81% at 1 mmol/L (Buening *et al*., 1981). Quercetin was a potent uncoupler of P450 reactions, acting by dissociation of the reduced P450–oxygen complex, and increased the rate of hydrogen peroxide formation by almost twofold (Sousa & Marletta, 1985).

In liver nuclei isolated from male Sprague-Dawley rats, quercetin caused a concentration-dependent increase in DNA damage and lipid peroxidation and a concentration-dependent decrease in nuclear glutathione content and glutathione *S*-transferase activity (Sahu & Washington, 1991; Sahu & Gary, 1996).

Quercetin was reported to have 1% of the oestrogenic activity of oestradiol in HeLa cells transfected with the human oestrogen receptor and the pERE-TK-CAT reporter plasmid (Santti *et al*., 1997).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Groups of 8–12 pregnant rats received 0, 2, 20, 200 or 2000 mg/kg bw quercetin on day 9 or on days 6–15 of gestation by oral gavage. No overt signs of toxicity were observed in the dams at any dose. Quercetin did not affect embryonic viability or morphology but fetal growth retardation was seen after exposure to 200 or 2000 mg/kg bw on day 9 and to 2 or 2000 mg/kg bw on days 9–15 (Wilhite, 1982).

4.4 Genetic and related effects

The genotoxicity of quercetin has been reviewed (Brown, 1980).

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 2 for references)

Quercetin induced DNA damage and SOS repair in bacterial cells. It did not induce differential toxicity in DNA repair-deficient strains of *Samonella*. It was mutagenic in several strains of *Salmonella typhimurium* and *Escherichia coli* in the absence of exogenous metabolic activation. In single studies, quercetin induced gene conversion but not gene mutation in *Saccharomyces cerevisiae* and induced sex-linked recessive lethal mutation in *Drosophila melanogaster*. *In vitro*, it caused DNA unwinding in rat liver nuclei and induced DNA single-strand breaks in mouse lymphoma L5178Y cells, but it did not induce unscheduled DNA synthesis in rat hepatocytes. Quercetin consistently induced gene mutation at the *tk* locus in mammalian cells *in vitro*, but *hprt* locus mutants were induced in only one of four studies. Sister chromatid exchange was induced in three of four studies in Chinese hamster cells *in vitro*, and chromosomal aberrations were induced in several Chinese hamster cell lines and in a human cell line *in vitro*. It induced cell transformation in mammalian cells. It induced sister chromatid exchange, micronuclei and chromosomal aberrations in human lymphocytes *in vitro* with and without exogenous metabolic activation. Urine and faecal extracts of rats treated with quercetin were mutagenic to *Salmonella typhimurium* TA98. Micronuclei were not induced by quercetin administered *in vivo*, either in bone-marrow cells of mice in four studies, in peripheral blood cells of mice in one study or in bone-marrow cells of rats in one study. Chromosomal aberrations were not induced in bone-marrow cells of rats treated *in vivo* in one study. Dominant lethal effects were not induced in either male mice or male rats in a single study.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to quercetin may occur during its production and use in dyes and from its presence in a variety of fruits and vegetables.

Table 2. Genetic and related effects of quercetin

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SOS chromotest, *Escherichia coli* PQ37	+	+	2.7	Rueff *et al*. (1986)
SOS chromotest, *Escherichia coli* PQ37	+	+	16	Dayan *et al*. (1987)
SOS chromotest, *Escherichia coli* PQ37	(+)	(+)	10	Czeczot & Kusztelak (1993)
Salmonella typhimurium, DNA repair-deficient strains, differential toxicity	–	–	200 µg/plate	Czeczot & Kusztelak (1993)
Salmonella typhimurium TA100, reverse mutation	+	+	5 µg/plate	Stoewsand *et al*. (1984)
Salmonella typhimurium TA100, TA98, TA97, TA102, TA1538, reverse mutation	+	+	10 µg/plate	Czeczot *et al*. (1990)
Salmonella typhimurium TA100, TA98, TA1537, reverse mutation	+	+	25 µg/plate	Hardigree & Epler (1978)
Salmonella typhimurium TA100, TA98, reverse mutation	+	+	3 µg/plate	National Toxicology Program (1992)
Salmonella typhimurium TA100, TA102, reverse mutation	–	NT	100 µg/plate	Cross *et al*. (1996)
Salmonella typhimurium TA98, TA102, reverse mutation	+	+	5 µg/plate	Crebelli *et al*. (1987)
Salmonella typhimurium TA1538, TA1534, TA1978, TA94, D3052, reverse mutation	–	NT	150 µg/plate	Crebelli *et al*. (1987)
Salmonella typhimurium TA97, TA1537, reverse mutation	+	NT	5 µg/plate	Busch *et al*. (1986)
Salmonella typhimurium TA1535, reverse mutation	–	–	500 µg/plate	Hardigree & Epler (1978)
Salmonella typhimurium TA1535, reverse mutation	–	NT	100 µg/plate	Czeczot *et al*. (1990)
Salmonella typhimurium TA98, reverse mutation	+	NT	3 µg/plate	Cross *et al*. (1996)
Salmonella typhimurium TA98, reverse mutation	+	+	25 µg/plate	Ochiai *et al*. (1984)
Salmonella typhimurium TA98, reverse mutation	+	+	10 µg/plate	Hatcher & Bryan (1985)
Salmonella typhimurium TA98, reverse mutation	+	+	5.4 µg/plate	Rueff *et al*. (1986)
Salmonella typhimurium TA98, reverse mutation	+	+	2.5 µg/plate	Nguyen *et al*. (1989)

Table 2 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA98, reverse mutation	+	+	15 µg/plate	Vrijsen *et al*. (1990)
Escherichia coli K-12 343/113, reverse mutation, *nad* locus	+	NT	1000	Hardigree & Epler (1978)
Escherichia coli K-12 343/113, forward or reverse mutation, *gal* or *arg* loci	–	–	NR	Hardigree & Epler (1978)
Saccharomyces cerevisiae D4, gene conversion	+	NT	2000	Hardigree & Epler (1978)
Saccharomyces cerevisiae, XΛ4-8C*p*$^{-}$ forward mutation, CAN^{R}	–	–	10 000	Hardigree & Epler (1978)
Saccharomyces cerevisiae D4, reverse mutation	–	–	10 000	Hardigree & Epler (1978)
Drosophila melanogaster, sex-linked recessive lethal mutations	+		25 000	Watson (1982)
DNA single-strand breaks, mouse lymphoma L5178Y cells *in vitro*	+	NT	10	Meltz & MacGregor (1981)
DNA damage, rat liver nuclei *in vitro* (unwinding assay)	+	NT	6	Sahu & Washington (1991)
Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	NT	6	Cross *et al*. (1996)
Gene mutation, Chinese hamster ovary CHO-AT3-2 cells, *tk* locus *in vitro*	+	NT	9	Carver *et al*. (1983)
Gene mutation, Chinese hamster ovary CHO-AT3-2 cells, *hprt* locus *in vitro*	–	NT	15	Carver *et al*. (1983)
Gene mutation, Chinese hamster ovary CHO-AT3-2 cells, *hprt* locus *in vitro*	–	NT	15	Carver *et al*. (1983)
Gene mutation, Chinese hamster ovary cells, Na^{+}/K^{+} ATPase locus *in vitro*	–	NT	15	Carver *et al*. (1983)
Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	+	+	20	Maruta *et al*. (1979)

Table 2 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	–	89.4	van der Hoeven *et al*. (1984)
Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	+	10	Meltz & MacGregor (1981)
Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	(+)	–	17.8	van der Hoeven *et al*. (1984)
Gene mutation, mouse lymphoma L5178Y cells, *hprt* locus *in vitro*	–	–	44.7	van der Hoeven *et al*. (1984)
Gene mutation (recombination by DNA fingerprinting), other animal cells *in vitro*	+	NT	16.6	Suzuki *et al*. (1991)
Gene mutation, Chinese hamster lung cells, DT^R *in vitro*	+	NT	100	Nakayasu *et al*. (1986)
Sister chromatid exchange, Chinese hamster cells *in vitro*	(+)	NT	2.5	Kubiak & Rudek (1990)
Sister chromatid exchange, Chinese hamster ovary CHO-AT3-2 cells *in vitro*	+	?	15	Carver *et al*. (1983)
Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	–	–	22.3	van der Hoeven *et al*. (1984)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	+	+	0.67	National Toxicology Program (1992)
Micronucleus formation, Chinese hamster lung V79 cells *in vitro*	+	+	3	Caria *et al*. (1995)
Chromosomal aberrations, Chinese hamster Don-6 and B-131 fibroblasts *in vitro*	+	NT	5	Yoshida *et al*. (1980)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	NT	10	Kubiak & Rudek (1990)

Table 2 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Chromosomal aberrations, Chinese hamster lung V79 cells *in vitro*	+	+	9.8	Gaspar *et al.* (1994)
Chromosomal aberrations, Chinese hamster CHO-AT3-2 cells *in vitro*	+	NT	6	Carver *et al*. (1983)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	+	10.1	National Toxicology Program (1992)
Cell transformation, BALB/c 3T3 mouse cells	(+)	NT	15	Meltz & MacGregor (1981)
Cell transformation, BALB/c 3T3 mouse cells	(+)	NT	10	Tanaka *et al*. (1987)
Cell transformation, Syrian hamster embryo cells, focus assay	+	NT	5	Umezawa *et al*. (1977)
Sister chromatid exchange, human lymphocytes *in vitro*	+	+	10	Rueff *et al*. (1986)
Micronucleus formation, human lymphocytes *in vitro*	+[c]	+[c]	3	Caria *et al*. (1995)
Chromosomal aberrations, human lymphocytes *in vitro*	+	NT	8	Yoshida *et al*. (1980)
Chromosomal aberrations, human HE2144 fibroblasts *in vitro*	+	NT	1	Yoshida *et al*. (1980)
Urine from Fischer 344 rats in *Salmonella typhimurium* TA100	–	(+)	0.2% in diet, 9 w	Stoewsand *et al*. (1984)
Urine and faeces from Sprague-Dawley rats in *Salmonella typhimurium* TA98	+	+	500 ip or po × 1	Crebelli *et al*. (1987)
Micronucleus formation, mouse bone-marrow cells *in vivo*	–		1000 po or ip	MacGregor (1979) [abst]
Micronucleus formation, mouse bone-marrow cells *in vivo*	–		1000 po × 2	Aeschbacher (1982)
Micronucleus formation, CD-1 mouse bone marrow cells *in vivo*	–		558 ip × 1	Caria *et al*. (1995)
Micronucleus formation, mouse bone-marrow cells and peripheral blood erythrocytes *in vivo*	–		400 ip × 1	Ngomuo & Jones (1996)
Micronucleus formation, Wistar rat bone-marrow cells *in vivo*	–		0.1% diet × 1 w	Taj & Nagarajan (1996)

Table 2 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Chromosomal aberrations, Wistar rat bone-marrow cells *in vivo*	–		0.1% diet × 1 w	Taj & Nagarajan (1996)
Dominant lethal mutation, inbred Swiss mice	–		400 ip × 2	Aravindakshan *et al*. (1985)
Dominant lethal mutation, Wistar rats	–		300 ip × 2	Aravindakshan *et al*. (1985)

[a] +, positive; (+), weakly positive; –, negative; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; unless otherwise stated, in-vitro test, µg/mL; in-vivo test, mg/kg bw per day; NR, not reported; w, week; ip, intraperitoneal; po, oral
[c] Increased CREST-negative micronuclei

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Quercetin was tested in several studies in rats by oral administration in the diet and by topical application in mice. Carcinogenicity was seen in only two studies in rats. Quercetin increased the incidences of intestinal and urinary bladder tumours in one study, but this effect was not seen in subsequent studies. Quercetin produced a low but significant increase in the incidence of renal tubular neoplasms, primarily adenomas in male rats, which was observed only after step-sectioning of renal tissue. When tested in several two-stage models of organ carcinogenesis, quercetin did not significantly enhance tumour incidence, except that of renal tumours induced by oestradiol in a model in hamsters.

5.4 Other relevant data

Although the metabolism of quercetin appears to be similar in humans and rabbits (the same three metabolites were identified in urine), no information on rats or mice was available for comparison. No information was available on the toxicity of quercetin in humans.

Quercetin increased the frequency of DNA damage and lipid peroxidation in liver nuclei of rats *in vitro*. In long-term studies in rats, there were no treatment-related clinical signs of toxicity, but renal hyperplasia occurred in males.

Quercetin inhibited cytochrome P450 enzymes in both human and rodent microsomes *in vitro*.

Fetal growth retardation was observed in a study in rats exposed to quercetin by oral gavage.

No data were available on the genetic and related effects of quercetin in humans. It was not genotoxic in experimental systems *in vivo*. It produced cytogenetic damage in human and rodent cells *in vitro*, but conflicting results were obtained in assays for gene mutation. It was mutagenic to *Drosophila*.

5.5 Evaluation

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

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

Overall evaluation

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

6. References

Aeschbacher, H.U. (1982) The significance of mutagens in food. In: Sorsa, M. & Vainio, H., eds, *Mutagens in Our Environment*, New York, Alan R. Liss, pp. 349–362

Ambrose, A.M., Robbins, D.J. & DeEds, F. (1952) Comparative toxicities of quercetin and quercitrin. *J. Am. pharm. Assoc*., **41**, 119–122

Aravindakshan, M., Chauhan, P.S. & Sundaram, K. (1985) Studies on germinal effects of quercetin, a naturally occurring flavonoid. *Mutat. Res.*, **144**, 99–106

Balasubramanian S. & Govindasamy, S. (1996) Inhibitory effect of dietary flavonol quercetin on 7,12-dimenthylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. *Carcinogenesis*, **17**, 877–879

Barotto, N.N., López, C.B., Eymard, A.R,. Fernández Zapico, M.E. & Valentich, M.A. (1998) Quercetin enhances pretumorous lesions in the NMU model of rat pancreatic carcinogenesis. *Cancer Lett*., **129**, 1–6

Belt, J.A., Thomas, J.A., Buchsbaum, R.N. & Racker, E. (1979) Inhibition of lactate transport and glycolysis in Ehrlich ascites tumor cells by bioflavonoids. *Biochemistry*, **18**, 3506–3511

Booth, A.N., Murray, C.W., Jones, F.T. & DeEds, F. (1956) The metabolic fate of rutin and quercetin in the animal body. *J. biol. Chem.*, **223**, 251–257

Brown, J.P. (1980) A review of the genetic effects of naturally occurring flavonoids, anthraquinone and related compounds. *Mutat. Res*., **75**, 243–277

Budavari, S., ed. (1996) *The Merck Index*, 12th Ed., Whitehouse Station, NJ, Merck & Co., p. 1381

Buening, M.K., Chang, R.L., Huang, M.-T., Fortner, J.G., Wood, A.W. & Conney, A.H. (1981) Activation and inhibition of benzo(*a*)pyrene and aflatoxin B_1 metabolism in human liver microsomes by naturally occurring flavonoids. *Cancer Res.*, **41**, 67–72

Busch, D.B., Hatcher, J.F. & Bryan, G.T. (1986) Urine recovery experiments with quercetin and other mutagens using the Ames test. *Environ. Mutag.*, **8**, 393–399

Caria, H., Chaveca, T., Laires, A. & Rueff, J. (1995) Genotoxicity of quercetin in the micronucleus assay in mouse bone marrow erythrocytes, human lymphocytes, V79 cell line and identification of kinetochore-containing (CREST staining) micronuclei in human lymphocytes. *Mutat. Res.*, **343**, 85–94

Carver, J.H., Carrano, A.G. & MacGregor, J.T. (1983) Genetic effects of the flavonols quercetin, kampherol, and galangin in Chinese hamster ovary cells *in vitro*. *Mutat. Res.*, **113**, 45–60

Chang, R.L., Huang, M.-T., Wood, A.W., Wong, C.-Q., Newmark, H.L., Haruhiko, Y., Sayer, J.M., Jerina, D.M. & Conney, A.H. (1985) Effect of ellagic acid and hydroxylated flavonoids on the tumorigenicity of benzo[a]pyrene and (±)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene on mouse skin and in the newborn mouse. *Carcinogenesis*, **6**, 1127–1133

Chemical Information Services (1995) *Directory of World Chemical Producers 1995/96 Standard Edition*, Dallas, TX, p. 608

Crebelli, R., Aquilina, G., Falcone, E. & Carere, A. (1987) Urinary and faecal mutagenicity in Sprague-Dawley rats dosed with the food mutagens quercetin and rutin. *Food chem. Toxicol.*, **25**, 9–15

Cross, H.J., Tilby, M., Chipman, K., Fery, D.R. & Gescher, A. (1996) Effect of quercetin on the genotoxic potential of cisplatin. *Int. J. Cancer*, **66**, 404–408

Czeczot, H. & Kusztelak, J. (1993) A study of the genotoxic potential of flavonoids using short-term bacterial assays. *Acta biochim. pol.*, **40**, 549–554

Czeczot, H., Tudek, B., Kusztelak, J., Szymczyk, T., Dobrowolska, B., Glinkowska, G., Malinowski, J. & Strzelecka, H. (1990) Isolation and studies of the mutagenic activity in the Ames test of flavonoids naturally occurring in medical herbs. *Mutat. Res.*, **240**, 209–216

Dayan, J., Deguingand, S., Truzman, C. & Chevron, M. (1987) Application of the SOS chromotest to 10 pharmaceutical agents. *Mutat. Res.*, **187**, 55–66

Deschner, E.E., Ruperto, J., Wong, G. & Newmark, H.L. (1991) Quercetin and rutin as inhibitors of azoxymethanol-induced colonic neoplasia. *Carcinogenesis*, **12**, 1193–1196

Dunnick, J.K. & Hailey, J.R. (1992) Toxicity and carcinogenicity studies of quercetin, a natural component of foods. *Fundam. appl. Toxicol.*, **19**, 423–431

Fukushima, S., Hagiwara, A., Ogiso, T., Shibata, M. & Ito, N. (1983) Promoting effects of various chemicals in rat urinary bladder carcinogenesis initiated by *N*-nitroso-*n*-butyl-(4-hydroxybutyl)amine. *Food chem. Toxicol.*, **21**, 59–68

Gaspar, J., Rodrigues, A., Laires, A., Silva, F., Costa, S., Monteiro, M.J., Monteiro, C. & Rueff, J. (1994) On the mechanisms of genotoxicity and metabolism of quercetin. *Mutagenesis*, **9**, 445–449

Gross, M., Pfeiffer, M., Martini, M., Cambell, D., Slavin, J. & Potter, J. (1996) The quantitation of metabolites of quercetin flavonols in human urine. *Cancer Epidemiol. Biomarkers Prev.*, **5**, 711–720

Gugler, R., Leschik, M. & Dengler, H.J. (1975) Disposition of quercetin in man after single oral and intravenous doses. *Eur. J. clin. Pharmacol.*, **9**, 229–234

Hardigree, A.A. & Epler, L.L. (1978) Comparative mutagenesis of plant flavonoids in microbial systems. *Mutat. Res.*, **58**, 231–239

Hatcher, J.F. & Bryan, G.T. (1985) Factors affecting the mutagenic activity of quercetin for *Salmonella typhimurium* TA98: Metal ions, antioxidants and pH. *Mutat. Res.*, **148**, 13–23

Hirose, M., Fukushima, S., Sakata, T., Inui, M. & Ito, N. (1983) Effect of quercetin on two-stage carcinogenesis of the rat urinary bladder. *Cancer Lett.*, **21**, 23–27

Hirose, M., Masuda, A., Fukashima, S. & Ito, N. (1988) Effects of subsequent antioxidant treatment on 7,12-dimethylbenz[a]anthracene-initiated carcinogenesis of the mammary gland, ear duct and forestomach in Sprague–Dawley rats. *Carcinogenesis*, **9**, 101–104

van der Hoeven, J.C.M., Bruggeman, I.M. & Debets, F.M.H. (1984) Genotoxicity of quercetin in cultured mammalian cells. *Mutat. Res.*, **136**, 9–21

Hollman, P.C.H., Gaag, M.V.D., Mengelers, M.J.B., van Trijp, J.M.P., deVries, J.H.M. & Katan, M.B. (1996) Absorption and disposition kinetics of the dietary antioxidant quercetin in man. *Free Rad. Biol. Med.*, **21**, 703–707

Hollman, P.C.H., van Trijp, J.M.P., Mengelers, M.J.B., deVries, J.H.M. & Katan, M.B. (1997) Bioavailability of the dietary antioxidant flavonol quercetin in man. *Cancer Lett.*, **114**, 139–140

IARC (1983) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans*, Vol. 31, *Some Food Additives, Feed Additives and Naturally Occurring Substances*, Lyon, pp. 213–229

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, p. 71

Ishikawa, M., Oikawa, T., Hosokawa, M., Hamada, J., Morikawa, K. & Kobayashi, H. (1985) Enhancing effect of quercetin on 3-methylcholanthrene carcinogenesis in C57BL/6 mice. *Neoplasma*, **32**, 435–441

Ito, N., Hagiwara, A., Tamano, S., Kagawa, M., Shibata, M.-A., Kurata, Y. & Fukushima, S. (1989) Lack of carcinogenicity of quercetin in F344/DuCrj rats. *Jpn. J. Cancer Res.*, **80**, 317–325

Kato, K., Mori, H., Fujii, M., Bunai, Y., Nishikawa, A., Shima, H., Takahashi, M., Kawai, T. & Hirono, I. (1984) Lack of promotive effect of quercetin on methylazoxymethanol acetate carcinogenesis in rats. *J. toxicol. Sci.*, **9**, 319–325

Khan, W.A., Wang, Z.Y., Athar, M., Bickers, D.R. & Mukhtar H. (1988) Inhibition of the skin tumorigenicity of (±)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene by tannic acid, green tea polyhenols and quercetin in Sencar mice. *Cancer Lett.*, **42**, 7–12

Kubiak, R. & Rudek, Z. (1990) SCEs and chromosome aberrations in mammalian cells in vitro treated with quercetin. *Acta biol. hung.*, **41**, 121–124

Lang, D.R. & Racker, E. (1974) Effects of quercetin and F_1 inhibitor on mitochondrial ATPase and energy-linked reactions in submitochondrial particles. *Biochim. biophys. Acta*, **333**, 180–186

Lide, D.R., ed. (1997) *CRC Handbook of Chemistry and Physics*, 78th Ed., Boca Raton, FL, CRC Press, p. 3-78

Long, G.D., DeChatelet, L.R., O'Flaherty, J.T., McCall, C.E., Bass, D.A., Shirley, P.S. & Parce, J.W. (1981) Effects of quercetin on magnesium-dependent adenosine triphosphatase and the metabolism of human polymorphonuclear leukocytes. *Blood*, **57**, 561–566

MacGregor, J.T. (1979) Mutagenicity studies of flavonoids *in vivo* and *in vitro* (Abstract No. 94). *Toxicol. appl. Pharmacol.*, **48**, A47

Maruta, A., Enaka, K. & Umeda, M. (1979) Mutagenicity of quercetin and kaempferol on cultured mammalian cells. *Gann*, **70**, 273–276

Matsukawa, Y., Nishino, H., Okuyama, Y., Matsui, T., Matsumoto, T., Matsumura, S., Shimizu, Y., Sowa, Y. & Sakai, T. (1997) Effects of quercetin and/or restraint stress on formation of aberrant crypt foci induced by azoxymethane in rat colons. *Oncology*, **54**, 118–121

Meltz, M.L. & MacGregor, J.T. (1981) Activity of the plant flavonol quercetin in the mouse lymphoma L5178Y $TK^{+/-}$ mutation, DNA single-strand break, and Balb/c 3T3 chemical transformation assays. *Mutat. Res.*, **88**, 317–324

Moon, J.-Y., Lee, D.-W. & Park, K.-H. (1998) Inhibition of 7-ethoxycoumarin *O*-deethylase activity in rat liver microsomes by naturally occurring flavonoids: Structure–activity relationships. *Xenobiotica*, **28**, 117–126

Mukhtar, H., Das, M., Khan, W. A., Wang, Z. Y., Bik, D. P. & Bickers, D. R. (1988) Exceptional activity of tannic acid among naturally occurring plant phenols in protecting against 7,12-dimethylbenz(*a*)anthracene-, benzo(*a*)pyrene-, 3-methylcholanthrene-, and *N*-methyl-*N*-nitrosourea-induced skin tumorigenesis in mice. *Cancer Res.*, **48**, 2361–2365

Nakayasu, M., Sakamoto, H., Terada, M., Nagao, M. & Sugimura, T. (1986) Mutagenicity of quercetin in Chinese hamster lung cells in culture. *Mutat. Res.*, **174**, 79–83

National Toxicology Program (1991) *NTP Chemical Repository Data Sheet: Quercetin*, Research Triangle Park, NC

National Toxicology Program (1992) *Toxicology and Carcinogenesis Studies of Quercetin (CAS No. 117-39-5) in F344/N Rats (Feed Studies)* (Tech. Rep. Ser. No. 409; NIH Publ. No. 92-3140), Research Triangle Park, NC

Ngomuo, A.J. & Jones, R.S. (1996) Genotoxicity studies of quercetin and shikimate *in vivo* in the bone marrow of mice and gastric mucosal cells of rats. *Vet. hum. Toxicol.*, **38**, 176–180

Nguyen, T., Fluss, L., Madej, R., Ginther, C. & Leighton, T. (1989) The distribution of mutagenic activity in red, rose and white wines. *Mutat. Res.*, **223**, 205–212

Nishino, H., Iwashima, A., Fujiki, H. & Sugimura, T. (1984) Inhibition by quercetin of the promoting effect of teleocidin on skin papilloma formation in mice initiated with 7,12-dimethylbenz[*a*]anthracene. *Gann*, **75**, 113–116

Ochiai, M., Nagao, M., Wakabayashi, K. & Sugimura, T. (1984) Superoxide dismutase acts as an enhancing factor for quercetin mutagenesis in rat-liver cytosol by preventing its decomposition. *Mutat. Res.*, **129**, 19–24

Podhajcer, O.L., Friedlander, M. & Graziani, Y. (1980) Effect of liposome-encapsulated quercetin on DNA synthesis, lactate production, and cyclic adenosine 3′:5′-monophosphate level in Ehrlich ascites tumor cells. *Cancer Res.*, **40**, 1344–1350

Rueff, J., Laires, A., Borba, H., Chaveca, T., Gomes, M.I. & Halpern, M. (1986) Genetic toxicology of flavonoids: The role of metabolic conditions in the induction of reverse mutation, SOS functions and sister chromatid exchanges. *Mutagenesis*, **1**, 179–183

Sahu, S.C. & Gray, G.C. (1996) Pro-oxidant activity of flavonoids: effects on glutathione and glutathione *S*-transferase in isolated rat liver nuclei. *Cancer Lett.*, **104**, 193–196

Sahu, S.C. & Washington, M.C. (1991) Quercetin-induced lipid peroxidation and DNA damage in isolated rat-liver nuclei. *Cancer Lett.*, **58**, 75–79

Santti, R., Makela, S., Strauss, L., Korkman, J. & Kostian, M. (1997) Phytoestrogens: Potential endocrine disruptors in males. *Toxicol. ind. Health*, **14**, 233–237

Sato, H., Takahashi, M., Furukawa, F., Miyakawa, Y., Hasegawa, R., Toyoda, K. & Hayashi, Y. (1987) Initiating potential of 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2), butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and 3,3′,4′,5,7-pentahydroxyflavone (quercetin) in two-stage mouse skin carcinogenesis. *Cancer Lett.*, **38**, 49–56

Siess, M.-H., Leclerc, J., Canivenc-Lavier, M.-C., Rat, P. & Suschetet, M. (1995) Heterogenous effects of natural flavonoids on monooxygenase activities in human and rat liver microsomes. *Toxicol. appl. Pharmacol.*, **130**, 73–78

Sousa, R.L. & Marletta, M.A. (1985) Inhibition of cytochrome *P*-450 activity in rat liver microsomes by the naturally occurring flavonoid, quercetin. *Arch. Biochem. Biophys.*, **240**, 345–357

Stoewsand, G.S., Andeerson, J.L., Boyd, J.N. & Hrazdina, G. (1984) Quercetin: A mutagen, not a carcinogen, in Fischer rats. *J. Toxicol. environ. Health*, **14**, 105–114

Sullivan, M., Follis, R.H., Jr & Hilgartner, M. (1951) Toxicology of podophyllin. *Proc. Soc. exp. Biol. Med.*, **77**, 269–272

Suolinna, E.-M., Buchsbaum, R.N. & Racker, E. (1975) The effect of flavonoids on aerobic glycolysis and growth of tumor cells. *Cancer Res.*, **35**, 1865–1872

Suzuki, S., Takada, T., Sugawara, Y., Muto, T. & Kominami, R. (1991) Quercetin induces recombinational mutations in cultured cells as detected by DNA fingerprinting. *Jpn. J. Cancer Res.*, **82**, 1061–1064

Taj, S. & Nagarajan, B. (1996) Inhibition by quercetin and luteolin of chromosomal aberrations induced by salted, deep-fried fish and mutton in rats. *Mutat. Res.*, **369**, 97–106

Takanashi, H., Aiso, S. & Hirono, I. (1983) Carcinogenicity test of quercetin and kaempferol in rats by oral administration. *J. Food Saf.*, **5**, 55–60

Tanaka, K., Ono, T. & Umeda, M. (1987) Pleiotropic effects of quercetin on the transformation of BALB 3T3 cells. *Jpn. J. Cancer Res.*, **78**, 819–825

Ueno, I., Nakano, N. & Hirono, I. (1983) Metabolic fate of [^{14}C]quercetin in the ACI rat. *Jpn. J. exp. Med.*, **53**, 41–50

Umezawa, K., Matsushima, T., Sugimura, T., Hirakawa, T., Tanaka, M., Katoh, Y. & Takayama, S. (1977) *In vitro* transformation of hamster embryo cells by quercetin. *Toxicol. Lett.*, **1**, 175–178

Verma, A.K., Johnson, J.A., Gould, M.N. & Tanner M.A. (1988) Inhibition of 7,12-dimethylbenz(*a*)anthracene- and *N*-nitrosomethylurea-induced rat mammary cancer by dietary flavonol quercetin. *Cancer Res.*, **48**, 5754–5758

Vrijsen, R., Michotte, Y. & Boeye, A. (1990) Metabolic activation of quercetin mutagenicity. *Mutat. Res.*, **232**, 243–248

Watson, W.A.F. (1982) The mutagenic activity of quercetin and kaempferol in *Drosophila melanogaster*. *Mutat. Res.*, **103**, 145–147

WHO (1993) *Guidelines for Drinking Water Quality*, 2nd Ed., Vol. 1, *Recommendations*, Geneva

Wilhite, C.C. (1982) Teratogenic potential of quercetin in the rat. *Food Cosmet. Toxicol.*, **20**, 75–79

Yoshida, M.A., Sasaki, M., Sugimura, K. & Kawachi, T. (1980) Cytogenetic effects of quercetin on cultured mammalian cells. *Proc. Jpn. Acad. Ser. B*, **56**, 443–447

Zhu, B.T. & Liehr, J.G. (1994) Quercetin increases the severity of estradiol-induced tumorigenesis in hamster kidney. *Toxicol. appl. Pharmacol.*, **125**, 149–158

Zhu, B.T., Ezell, E.L. & Liehr, J.G. (1994) Catechol-*O*-methyltransferse-catalyzed rapid *O*-methylation of mutagenic flavonoids. *J. biol. Chem.*, **269**, 292–299