HYDROQUINONE

Data were last reviewed in IARC (1977) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

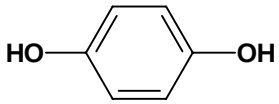
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 123-31-9
Chem. Abstr. Name: 1,4-Benzenediol
IUPAC Systematic Name: Hydroquinone
Synonym: Benzoquinol

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_6H_6O_2$ Relative molecular mass: 110.11

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Hexagonal prisms (Verschueren, 1996)
(*b*) *Boiling-point*: 287°C (Lide, 1997)
(*c*) *Melting-point*: 172.3°C (Lide, 1997)
(*d*) *Solubility*: Soluble in water, ethanol and diethyl ether (Lewis, 1993)
(*e*) *Vapour pressure*: 532 Pa at 150°C; relative vapour density (air = 1), 3.81 (Verschueren, 1996)
(*f*) *Flash-point:* 165°C, closed cup (American Conference of Governmental Industrial Hygienists, 1992)
(*g*) *Conversion factor*: $mg/m^3 = 4.5 \times ppm$

1.2 Production and use

In 1992, world production of hydroquinone was approximately 35 thousand tonnes (United States, 16; Europe, 11; Japan, 6; Central and South America and Asian countries other than Japan, 2) (WHO, 1994).

Hydroquinone is used as a photographic developer (with black-and-white film), a dye intermediate, a stabilizer in paints, varnishes, motor fuels and oils, an antioxidant for fats and oils, an inhibitor of polymerization and in the treatment of skin hyperpigmentation (Lewis, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), approximately 100 000 workers in the United States were potentially exposed to hydroquinone (see General Remarks). Occupational exposures to hydroquinone may occur in its production and use in the production of dyes, paints, motor fuels and oils, and some polymers. Dermal contact with hydroquinone may occur in the development of black-and-white photographs.

1.3.2 *Environmental occurrence*

Hydroquinone is both a natural and an anthropogenic compound. It occurs naturally as a conjugate with β-D-glucopyranoside in the leaves, bark and fruit of a number of plants, especially the ericaceous shrubs such as cranberry, cowberry, bearberry and blueberry. It may be released to the environment as a fugitive emission during its production, formulation and use as a chemical intermediate, photographic chemical and stabilizer (United States National Library of Medicine, 1997). Users of skin-bleaching formulations may be exposed to hydroquinone.

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 2 mg/m^3 as the 8-h time-weighted average threshold limit value for occupational exposures to hydroquinone in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

No international guideline for hydroquinone in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

One of the most prominent uses of hydroquinone is in photographic development and it is possible that work as a photographic processor often involved hydroquinone exposure in the past. Several studies have examined cancer risks among photographic processors. However, the Working Group did not use these except where the report provided some information indicating that the workers concerned had indeed been exposed to hydroquinone.

2.1 Cohort studies

Pifer *et al*. (1995) reported a cohort mortality study of 879 workers (22 895 person–years of follow-up) at a Tennessee (United States) plant in which hydroquinone was manufactured and used over several decades. Job history records were linked to extensive industrial hygiene data and expertise to estimate cumulative exposure to hydroquinone. Average hydroquinone dust levels ranged from 0.1 to 6.0 mg/m^3, with levels over 2 mg/m^3 for most of the period of operation of the plant. Mean employment duration was 13.7 years and mean follow-up from first exposure was 26.8 years. Relative risk estimates (standardized mortality ratios (SMRs)) for this cohort were derived by comparison with the general population of Tennessee as well as with an occupational cohort not exposed to hydroquinone (a plant of the same company, located in New York State). The SMR for all causes of death combined (n = 168) was significantly below 1.0, as was the SMR for all cancers combined (n = 33). Only two sites, colon (n = 5) and lung (n = 14) had more than three observed cases. Most site-specific SMRs were well below 1.0. The results were similar with both comparison populations. The dose–response analyses of selected cancer sites did not reveal any meaningful trend or heterogeneity. [The numbers for individual cancer sites were small and the power to detect effects was weak. The Working Group noted that this cohort had systematically lower SMRs than the comparison industrial cohort.]

Nielsen *et al*. (1996) carried out a cohort incidence study among 837 Danish lithographers born between 1933 and 1942 and registered with the Danish Union of Lithographers in 1974 or later. Questionnaires were sent to cohort members in 1989 to obtain information on job exposures; usable responses were received from 620 workers. About one-quarter of the cohort members reported working regularly with hydroquinone for photographic development. The entire cohort was traced in the Danish Cancer Registry from 1974 to 1989. Relative risk estimates (standardized incidence ratios (SIRs)) for this cohort were derived by comparison with the general population of Denmark. There were a total of 24 cancers registered, giving an SIR of 0.9. For no site except skin were there more than three cases. Five cases of malignant melanoma occurred, with 1.5 expected (SIR, 3.4; 95% confidence interval, 1.2–7.5). Among these five, two had reportedly been exposed to hydroquinone.

3. Studies of Cancer in Experimental Animals

In skin painting studies in mice, hydroquinone was inactive as an initiator of skin carcinogenesis. In bladder implantation studies, hydroquinone in cholesterol pellets increased the incidence of bladder carcinomas in mice (IARC, 1977).

3.1 Oral administration

3.1.1 *Mouse*

Groups of 55 male and 55 female B6C3F$_1$ mice, eight to 10 weeks of age, were administered 0, 50 or 100 mg/kg bw hydroquinone (purity, > 99%) by gavage on five days per

week for 103 weeks. Mean body weights of high-dose mice at the end of the study were lower than those of vehicle controls, and the relative liver weights were increased for exposed males and high-dose females. Survival in treated mice was similar to that in controls. No increase in tumours was found in exposed males. In females, hepatocellular adenomas were found in 2/55 controls, 15/55 low-dose group ($p = 0.001$) and 12/55 high-dose group ($p = 0.005$) (United States National Toxicology Program, 1989).

Groups of 28–30 male and 28–30 female B6C3F$_1$ mice, six weeks of age, were given hydroquinone (purity, > 99%) in the diet at concentrations of 0 or 0.8% for 96 weeks. The final body weight was reduced in hydroquinone-treated females. The incidence of hepatocellular adenoma was increased to 14/30 in exposed males ($p < 0.05$) compared with 6/28 in controls. Incidence of no other tumour type was significantly increased by exposure in males, although three renal adenomas occurred. No increase in tumour incidence was found in females (Shibata *et al*., 1991).

3.1.2 *Rat*

Groups of 55 male and 55 female Fischer 344/N rats, seven to nine weeks of age, were administered 0, 25 or 50 mg/kg bw hydroquinone (purity, > 99%) by gavage on five days per week for 103 weeks. Mean body weights of exposed males were reduced and the relative kidney weights for high-dose males were greater than those for vehicle controls. Survival was reduced in exposed animals. In exposed males, renal tubule cell adenomas developed in 4/55 low-dose group ($p = 0.069$) and 8/55 high-dose group ($p = 0.003$) compared with 0/55 controls. In exposed females, mononuclear cell leukaemia developed in 15/55 low-dose group ($p = 0.048$) and 22/55 high-dose group ($p = 0.003$) compared with 9/55 controls. The historical incidence of leukaemia for water/vehicle control female rats was 25 ± 15% (United States National Toxicology Program, 1989). [The Working Group noted that the incidences of leukaemia in the exposed group were within the historical control range.]

Groups of 30 male and 30 female Fischer 344 rats, six weeks of age, were given hydroquinone (purity, > 99%) in the diet at concentrations of 0 or 0.8% for 104 weeks. Body weight gain was decreased in both exposed males and females. Chronic nephropathy was more severe in males given hydroquinone. In the kidneys of exposed male rats, the incidence of tubule hyperplasia was 30/30 (100%) and that of adenomas was 14/30 (47%; $p < 0.01$), compared with 1/30 (3%) and 0/30 (0%), respectively in unexposed controls. Incidence of no other tumour type was increased by exposure (Shibata *et al*., 1991).

3.2 Administration with known carcinogens

3.2.1 *Rat*

Groups of 15 male Fischer 344 rats, six weeks of age, were administered 0 or 0.05% *N*-nitrosobutyl-*N*-(4-hydroxybutyl)amine in the drinking-water for two weeks followed by ureteric ligation one week later to initiate bladder carcinogenesis. Hydroquinone [purity unspecified] was administered at concentrations of 0 or 0.2% in the diet for 22

weeks and all animals were killed at week 24. Hydroquinone alone induced no bladder lesions. When hydroquinone was given after initiation, no increase in bladder lesions was observed (Miyata *et al*., 1985).

Groups of 10 or 15 male Fischer 344 rats, six weeks of age, were given hydroquinone (purity > 99%) at concentrations of 0 or 0.8% in the diet for 51 weeks, while other groups of 15 or 16 animals were fed 0 or 0.8% hydroquinone for 51 weeks starting one week after exposure to 150 mg/kg bw *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine by oral gavage to initiate stomach carcinogenesis. The body weights of rats given hydroquinone after initiator were lower than those given only initiator. Hydroquinone alone did not induce forestomach lesions, nor did it enhance the incidence of forestomach or glandular stomach lesions induced by the initiator (Hirose *et al*., 1989).

Groups of 7–10 male Sprague-Dawley rats, weighing 200 g, were given hydroquinone (purity, > 99%) in the diet at concentrations of 0, 100 or 200 mg/kg for six weeks beginning one week after partial hepatectomy and intraperitoneal injection of 300 mg/kg bw *N*-nitrosodiethylamine to initiate liver carcinogenesis. One group underwent only partial hepatectomy and was fed the high dose of hydroquinone. In the hepatectomized group exposed only to hydroquinone, no liver enzyme-altered (γ-glutamyltranspeptidase) foci were induced. Hydroquinone after initiation increased the multiplicity of foci from 0.08 per cm^2 to 0.68 in the low-dose group and to 0.34 in the high-dose group [statistical analysis not given]. In a second experiment, groups of 10 rats underwent the regimen to initiate liver carcinogenesis and received 0 or 1 mg/kg bw hydroquinone by oral gavage on five days per week for seven weeks. Hydroquinone did not increase the multiplicity of enzyme-altered foci, but their area was increased from a mean of 1.00×10^{-4} cm^2 to 1.30×10^{-4} cm^2 ($p < 0.05$) and their volume from 1.49×10^{-4} cm^3 to 3.12×10^{-4} cm^3 ($p < 0.01$) (Stenius *et al*., 1989).

Groups of 15 or 12 male Fischer 344 rats, seven to eight weeks of age, were given hydroquinone (purity, > 99%) at concentrations of 0 or 0.8% in the diet for 49 weeks alone or starting one week after six intraperitoneal injections of 25 mg/kg bw *N*-nitrosomethyl-*n*-amylamine to initiate upper digestive tract carcinogenesis. Hydroquinone alone reduced weight gain. In animals given hydroquinone after carcinogen, the incidence of oesophageal carcinoma was 4/12 rats (not significant) compared with 0/11 in the group given initiator only, and the multiplicity was increased to 0.33 tumours per rat ($p < 0.05$) compared with 0 in the controls (Yamaguchi *et al*., 1989).

Groups of 10 or 20 male Fischer 344/Du Crj rats [age unspecified] were given hydroquinone [purity unspecified] at concentrations of 0 or 0.8% in the diet for 30 weeks either alone or after exposure to 0.1% *N*-nitroso-bis(2-hydroxypropyl)amine in the drinking-water for two weeks to initiate carcinogenesis in several organs. No unexposed controls were included. Body weight was reduced by hydroquinone given after the initiator and liver weight was increased compared with the group given initiator only. Hydroquinone alone induced no lung or thyroid tumours. Rats given initiator developed low incidences of tumours in the thyroid, lung, urinary bladder and kidney. None of these incidences was increased by hydroquinone (Hasegawa *et al*., 1990).

Groups of 10 or 20 male Fischer 344 rats, six weeks of age, were given hydroquinone (purity, > 99%) in the diet at a concentration of 0.8% for 36 weeks alone or after exposure to 0.05% *N*-nitrosobutyl-*N*-(4-hydroxybutyl)amine in the drinking-water for four weeks to initiate bladder carcinogenesis. Hydroquinone alone did not affect body weight or bladder weight. Hydroquinone exposure alone did not induce bladder tumours and feeding of hydroquinone after initiator did not increase the incidence or multiplicity of bladder neoplasms induced by the initiatior alone (Kurata *et al*., 1990).

Groups of 15 or 20 male Wistar/Crj rats, six weeks of age, were given hydroquinone [purity unspecified] at concentrations of 0 or 0.8% in the diet for 36 weeks starting one week after exposure to 0.1% *N*-nitrosoethyl-*N*-hydroxyethylamine in the drinking-water for three weeks to initiate liver and kidney carcinogenesis. The final body weights of rats given hydroquinone were lower than those of animals given only basal diet or initiation. The relative liver and kidney weights of rats receiving hydroquinone were higher than those of the basal diet group. Hydroquinone alone did not induce preneoplastic or neoplastic liver or kidney lesions. In the kidney, hydroquinone exposure after initiation increased the multiplicity of renal cell tumours to 5.22 per rat ($p < 0.01$) compared with 2.58 after initiation only and increased the multiplicity of microadenomas to 2.77 ($p < 0.05$) compared with 0.94 after initiation only (Okazaki *et al*., 1993).

3.2.2 *Hamster*

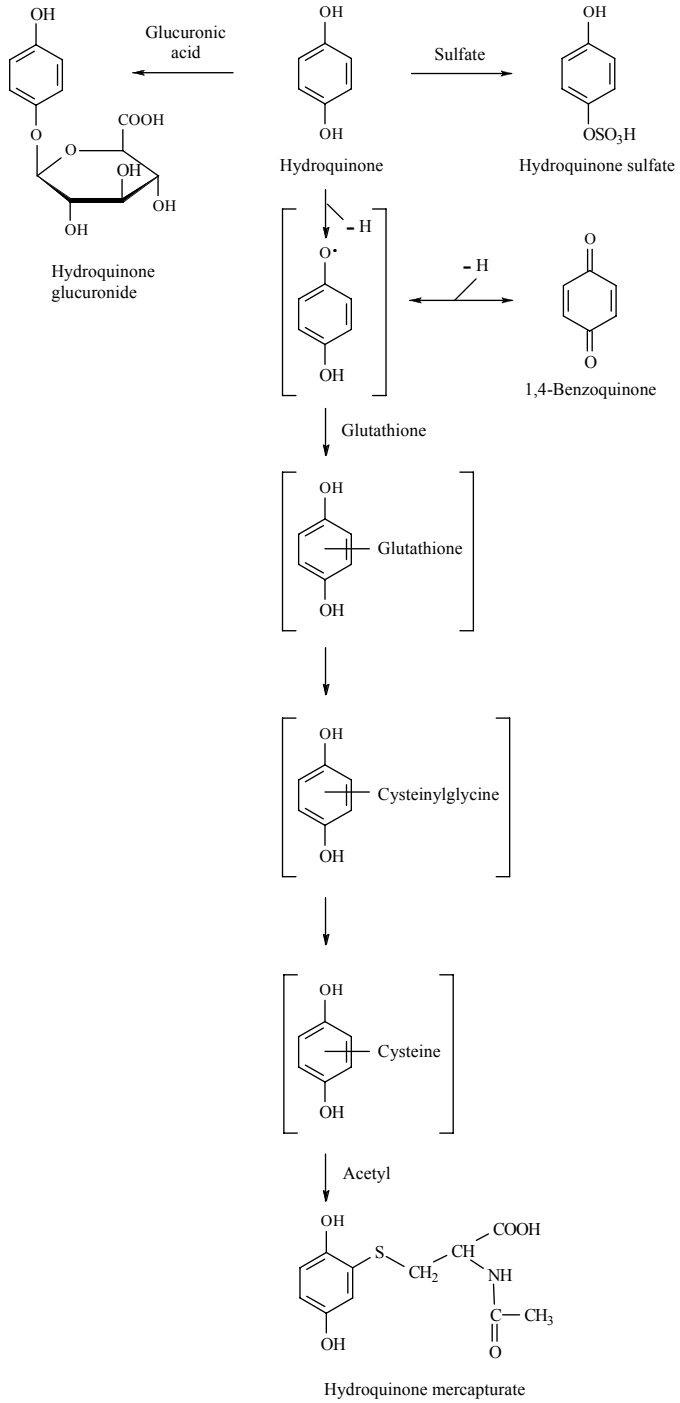
Groups of female Syrian golden hamsters, six weeks of age, were given hydroquinone (purity, > 99%) at concentrations of 0 or 1.5% in the diet for 16 weeks either alone (10 and 15 hamsters) or after two subcutaneous injections of 70 mg/kg bw *N*-nitrosobis(2-oxopropyl)amine (20 hamsters) to initiate pancreatic carcinogenesis. Hydroquinone alone did not affect body weights or liver or pancreas weights compared with untreated controls. Given after the initiator, hydroquinone did not affect body weight or liver weight, but reduced pancreas weight compared with hamsters given only initiator. Hydroquinone alone did not induce neoplastic lesions in the pancreas or liver. In hamsters given hydroquinone after initiator, the multiplicity of pancreatic lesions was reduced (Maruyama *et al*., 1991).

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

4.1 Absorption, distribution, metabolism and excretion

The major metabolism of hydroquinone is to the sulfate and, at higher exposure, glucuronide conjugates. Oxidation to 1,4-benzoquinone results in a reactive metabolite, that may form mono- or polyglutathione conjugates (see Figure 1).

Figure 1. Proposed metabolism of hydroquinone



From WHO (1994)

4.1.1 *Humans*

Rates of percutaneous absorption of hydroquinone in 5% aqueous solution through human stratum corneum *in vitro* were approximately half those through full-thickness rat skin; the human skin penetration rate was classified as 'slow' (Barber *et al*., 1995). The data allowed calculation of skin absorbance in workers in photographic development.

Rates of hydroquinone glucuronidation in human liver microsomes showed a two- to three-fold variation between individual liver samples; they were somewhat higher than in the rat, and lower than in the mouse liver (Seaton *et al*., 1995). A compartmental pharmacokinetic model was derived to describe the pharmacokinetics of hydroquinone *in vivo* in humans, rats and mice, incorporating hydroquinone glucuronidation rates; sulfation of hydroquinone was not included in this model. NAD(P)H:quinone acceptor oxidoreductases protect against reactive quinones by reducing them to the hydroquinone; this enzyme seems to be absent in some individuals, which will lead to loss of such protection and make them more sensitive to hydroquinone toxicity (Ross, 1996).

4.1.2 *Experimental systems*

Percutaneous absorption of hydroquinone from an aqueous solution was studied in full-thickness rat skin *in vitro*; the permeability constant was 2.3×10^{-5} cm/h, which was approximately two-fold faster than that of human skin (Barber *et al*., 1995).

The disposition of [^{14}C]hydroquinone after oral administration to Sprague-Dawley rats was studied by Divincenzo *et al*. (1984). Whether mixed with the diet or administered as a single dose, the compound was almost completely excreted in urine, with up to 4% in the faeces. By far the major metabolites were the sulfate and glucuronide conjugates, with a small amount of unconjugated hydroquinone. Apparently no analysis for mercapturates was performed. These results were confirmed by Saito and Takeichi (1995), who also demonstrated a wide tissue distribution of hydroquinone. Hill *et al*. (1993) found appreciable amounts of hydroquinone–glutathione conjugates in bile after intraperitoneal administration of hydroquinone to rats that had been pretreated with AT-125, an inhibitor of γ-glutamyltranspeptidase: both mono-, di- and triglutathione conjugates were found, as well as a mercapturate in urine. More than 4% of the dose was recovered as glutathione conjugates, indicating considerable formation of the highly toxic 1,4-benzoquinone (see this volume) metabolite. Nerland and Pierce (1990) identified the hydroquinone mercapturate (*N*-acetyl-*S*-(2,5-dihydroxyphenol)-L-cysteine) in untreated rats after administration of hydroquinone.

A simple compartmental pharmacokinetic model was proposed by Seaton *et al*. (1995) to describe the pharmacokinetics of hydroquinone in mice, rats and humans. The model did not include hydroquinone sulfation, which does occur in rats and possibly in mice, although glucuronidation is the major reaction. Phenol and hydroquinone may mutually inhibit their sulfation if both are present simultaneously in the rat (Legathe *et al*., 1994).

Hydroquinone can be converted to the very reactive 1,4-benzoquinone by several enzymes. A major activity is myeloperoxidase (Subrahmanyam *et al*., 1991), which is

stimulated by phenol and some other phenols. Microsomal cytochrome P450 may also play a role (Hill *et al*., 1993). Macrophage peroxidase activity converting hydroxyquinone to 1,4-benzoquinone may be important in the myelotoxicity of benzene (Schlosser & Kalf, 1989; Smith *et al*., 1989; Snyder & Hedli, 1996). Copper(II) ions strongly enhance this process, in which hydrogen peroxide and other reactive oxygen species may be involved (Eyer, 1991; Rao, 1991; Li & Trush, 1993a,b).

Hydroquinone forms DNA adducts in the peroxidase-containing promyelocytic HL-60 cell line; this process is enhanced by addition of hydrogen peroxide or cumene hydroperoxide (Lévay & Bodell, 1996), presumably because the hydroquinone is oxidized by a cellular peroxidase to a reactive, DNA-binding metabolite.

4.1.3 *Comparison of human and rodent data*

The metabolism of hydroquinone seems very similar in man and rodents: sulfate and glucuronide conjugates are the major metabolites. Through the 1,4-benzoquinone metabolite, a reactive intermediate can be formed, in particular in macrophages by peroxidases, that may be trapped by conjugation with glutathione. The reactive intermediate may form DNA adducts, and may also be responsible for kidney toxicity.

4.2 Toxic effects

The toxicity of hydroquinone has been reviewed (WHO, 1994).

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Long-term feeding of hydroquinone to rats led to aplastic anaemia, liver cord-cell atrophy and ulceration of the gastric mucosa. A single high dose was reported to induce renal tubule necrosis in rats (IARC, 1977).

In a carcinogenicity study (United States National Toxicology Program, 1989; Kari *et al*., 1992), nephropathy was observed in nearly all male and most female rats of all dosed groups and vehicle controls. The nephropathy was characterized by degeneration and regeneration of tubule epithelium, atrophy and dilatation of some tubules, hyaline casts in the tubule lamina, glomerulosclerosis, interstitial fibrosis, and chronic inflammation. In males, the nephropathy was more severe in the high-dose (50 mg/kg bw per day) group, while in females no dose-dependence was observed. Nephropathy was observed in males also in 13-week studies. Presence of hyaline droplets was not reported. In another carcinogenicity study (Shibata *et al*., 1991), the prevalence and severity of chronic nephropathy was more marked in dosed males than in females. It was stated that the nephropathy observed was not of the α_{2u}-globulin nephropathy type. In a reanalysis of the histology of the United States National Toxicology Program study, it was observed that the atypical tubule hyperplasias and adenomas were located in areas of severe chronic progressive nephropathy (Hard *et al*., 1997).

After six weeks of oral administration (50 mg/kg bw per day) of hydroquinone to male Fischer 344 rats, modestly elevated urinary excretion of alanine aminopeptidase, alkaline phosphatase, γ-glutamyltranspeptidase and *N*-acetylglucosaminidase was observed (English *et al*., 1994a). No such indication of renal toxicity was observed in female Fischer 344 rats or male Sprague-Dawley rats. Interstitial inflammation and degenerative/regenerative tubule foci were more frequent in high-dose (25 or 50 mg/kg bw/day) male Fischer 344 rats. Similarly, the proportion of proliferating cells, measured by bromodeoxyuridine (BrdU) labelling, was elevated in the proximal tubules in male Fischer 344 rats given the highest dose (50 mg/kg bw per day), while no consistent change in the labelling was observed in the renal tubules from male Sprague-Dawley or female Fischer 344 rats. On the other hand, after a single dose of hydroquinone (Boatman *et al*., 1996), female Fischer 344 rats were more sensitive to hydroquinone-induced nephrotoxicity, as measured by urinary excretion of alanine aminopeptidase, *N*-acetylglucosaminidase, alkaline phosphatase, γ-glutamyltranspeptidase, glucose and creatinine, by urinary osmolality or by blood levels of urea nitrogen. In these acute experiments, no nephrotoxicity was observed in Sprague-Dawley rats.

In 14-day studies (United States National Toxicology Program, 1989), tremors, convulsions and death following gavage were observed at doses ≥ 500 mg/kg bw per day. In 13-week studies, lethargy, tremor and convulsions leading to death were also observed at doses ≥ 200 mg/kg bw per day.

In a two-year study (United States National Toxicology Program, 1989; Kari *et al*., 1992), dose-dependent hepatic morphological changes (anisokaryosis, elevated frequency of multinucleated cells) were observed in male mice. In a long-term feeding study (0.8% in the diet) (Shibata *et al*., 1991), hepatic centrilobular hypertrophy was observed in males and forestomach hyperplasia in both males and females, while no non-neoplastic changes in the kidney were reported.

Administration of hydroquinone (0.5% in the diet) for 20 weeks did not induce hyperplasia or papillomatous lesions in the forestomach in Syrian golden hamsters (Hirose *et al*., 1986). In male Fischer 344 rats, oral administration of hydroquinone for eight weeks (0.8% in the diet) did not induce hyperplasia or DNA synthesis, as measured by BrdU-labelling index in the forestomach epithelium. No cell proliferation, increased DNA synthesis or increase in pepsinogen-isoenzyme-1-altered neoplastic foci was observed in the pyloric mucosa (Shibata *et al*., 1990).

A large number of studies have been performed on the effects of hydroquinone on bone marrow, in order to elucidate the mechanisms of the myelodepressive and leukaemogenic activity of benzene.

Hydroquinone decreased interleukin (IL)-1 secretion and protein and RNA synthesis of isolated human peripheral blood monocytes induced by *Escherichia coli* lipopolysaccharide at micromolar concentrations (Carbonnelle *et al*., 1995). Hydroquinone (4 μmol/L) inhibited the growth of bone marrow cells from female C57BL/6 × DBA/2 mice (Seidel *et al*., 1991) and from male Swiss Webster and C57BL/6J mice (10 μmol/L) (Neun *et al*., 1992). Hydroquinone (50, 75 or 100 mg/kg bw, single intraperitoneal admi-

nistration) decreased the incorporation of ^{59}Fe into erythrocytes in a dose-dependent fashion in female Swiss albino mice (Snyder *et al*., 1989).

Hydroquinone induced apoptosis in HL60 human promyelocytic leukaemia cells and $CD34^+$ human bone-marrow progenitor cells at concentrations (25 and 50 μmol/L, respectively) at which necrosis was negligible (Hiraku & Kawanishi, 1996; Moran *et al*., 1996). Hydroquinone (1 μmol/L) inhibited the phorbol myristyl acetate- and 1,25-dihydroxyvitamin D_3-induced differentiation of HL-60 cells to macrophages, but had no effect on IL-1-induced differentiation or on cell proliferation. Similarly, it did not affect the differentiation of HL-60 cells to granulocytes (Oliveira & Kalf, 1992). Hydroquinone (2 μmol/L) induced granulocytic differentiation of 32D.3(G) myeloblasts; it also stimulated granulocytic differentiation of myeloblasts *in vivo* in C57BL/6J mice after intraperitoneal injection of 25–50 mg/kg bw twice daily for two days (Hazel *et al*., 1996a) and increased the number of femoral granulocyte/macrophage colony-forming cells in mice after intraperitoneal injection (50–75 mg/kg bw twice daily for 11 days) (Henschler *et al*., 1996). Hydroquinone (at 1 μmol/L) enhanced the colony-forming response of murine bone-marrow cells stimulated with recombinant granulocyte/macrophage colony-stimulating factor (rGM-CSF) (Irons *et al*., 1992) and of factor-dependent cells Paterson (FDCP)–mix (at 10^{-9} mol/L) induced by granulocyte/macrophage colony-stimulating factor (Henschler *et al*., 1996). In human $CD34^+$ cells, a similar effect was observed at 10^{-21} mol/L concentrations of hydroquinone (Irons & Stillman, 1996a,b).

On the other hand, hydroquinone (3 μmol/L) prevented the staurosporine-induced apoptosis of HL-60 and the IL-3-dependent murine myeloblastic (32D) cell line; it also prevented apoptosis of the 32D cells observed in the absence of IL-3. The myeloperoxidase inhibitor indomethacin opposed the effect of hydroquinone on staurosporine-induced apoptosis of HL-60 cells (Hazel *et al*., 1995, 1996b). Pretreatment of human leukaemia cells ML-1 with buthionine sulfoximine (100 μmol/L for 24 h), in order to decrease their glutathione content, increased the susceptibility of these cells to hydroquinone-induced inhibition of differentiation caused by phorbol acetate; pretreatment with 1,2-dithiole-3-thione, which induces reduced glutathione synthesis, prevented the differentiation inhibition of hydroquinone. Treatment of DBA/2 mice with 1,2-dithiole-3-thione, which increased the activity of quinone reductase of bone-marrow stromal cells by 50%, decreased the susceptibility of these cells towards hydroquinone (Trush *et al*., 1996).

Hydroquinone (50 μmol/L) induced a cytosol-to-membrane translocation of protein kinase C, followed by inactivation of the enzyme activity, in cultured LL/2 lung carcinoma cells (Gopalakrishna *et al*., 1994).

Hydroquinone (1–10 μmol/L) induced fluorescence from 2′,7′-dichlorofluorescin acetate in HL-60 human leukaemia cells; this was interpreted to indicate intracellular generation of hydrogen peroxide and other peroxides (Hiraku & Kawanishi, 1996). Hydroquinone (200 mg/kg bw, as a single oral dose) administered to male Sprague-Dawley rats induced a three-fold increase in urinary excretion of malonaldehyde, increased hepatic ornithine decarboxylase activity from a control value of 16.8 pmol/mg/h

to 86.5 pmol/mg/h and, *in vitro*, 0.3 mmol/L induced a rapid depletion (30%) of the glutathione content of isolated hepatocytes (Stenius *et al*., 1989). Hydroquinone (10 μmol/L) induced formation of 8-hydroxydeoxyguanosine in the DNA of HL-60 cells *in vitro*, but not in bone-marrow cells of $B6C3F_1$ mice *in vivo* after a single intraperitoneal dose of 75 mg/kg bw (Kolachana *et al*., 1993). An increase in urinary excretion of 8-hydroxyguanine was observed in rats given a single intraperitoneal dose of 11 mg/kg bw hydroquinone (Suzuki *et al*., 1995).

Hydroquinone (≥ 0.25 μmol/L) prevented the elimination by apoptosis of G418-resistant, transformed Swiss 3T3 MxCl1 cells by co-cultured TGF-β-treated C3H 10T½ Cl8 cells (Schaeffer *et al*., 1995).

In a study on the immunotoxic effects of cigarette tar components, hydroquinone, at a concentration that did not affect the viability of the cells (50 μmol/L), decreased IL-2-dependent DNA synthesis and cell proliferation by > 90% in cultured human T lymphoblasts (Li *et al*., 1997). Hydroquinone inhibited Fc-receptor-mediated phagocytosis in mouse peritoneal macrophages only at rather high concentrations (100 μmol/L) (Manning *et al*., 1994).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

In a developmental toxicity study in COBS-CD-BR rats dosed by gavage, hydroquinone (30, 100 or 300 mg/kg bw per day on days 6 through 15 of gestation) did not induce malformation, gross variations or skeletal variations, with the exception of an increase in the incidence of total common vertebral variations at the highest dose. At the highest dose, slight reductions of mean fetal body weight and of maternal body weight gain were also observed (Krasavagne *et al*., 1992).

In New Zealand white rabbits administered 25–150 mg/kg bw per day hydroquinone by gavage on days 6 through 18 of gestation, the only treatment-related changes observed were nonsignificant increases in minor skeletal malformations (vertebral/rib defects, angulated hyoid arch) and microphthalmia at the highest dose level, at which maternal weight gain was also decreased (Murphy *et al*., 1992).

In a two-generation reproductive toxicity study in rats, no adverse effect was observed on feed consumption, survival, reproductive parameters, pup weight, sex distribution, survival, gross lesions or microscopic anatomy after oral doses of 15–150 mg/kg bw per day (Blacker *et al*., 1993).

Hydroquinone had no adverse effect upon cultured whole rat conceptuses at a concentration of 50 μmol/L, but killed all embryos at 100 μmol/L (Chapman *et al*., 1994).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

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

Hydroquinone did not induce SOS repair and did not increase the numbers of mutants when tested against commonly used strains of *Salmonella typhimurium*. However, it was shown to be mutagenic to *S. typhimurium* TA104 and TA102, which are sensitive to oxidative mutagens. The activity demonstrated with TA104 was almost completely inhibited by co-incubation with superoxide dismutase and catalase and is consistent with superoxide and hydrogen peroxide being the mutagen(s). Hydroquinone induced gene conversion and mutations in *Saccharomyces cerevisiae*. It did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster*.

In cultured mammalian cells, hydroquinone induced DNA single-strand breaks in rat hepatocytes, gene mutations, chromosomal aberrations and sister chromatid exchanges. Positive results were obtained in a cell transformation assay using Syrian hamster embryo cells. Increased frequencies of CREST-positive micronuclei (indicating chromosome loss) and CREST-negative micronuclei (indicating chromosome breakage) were observed following exposure of Chinese hamster lung cells to hydroquinone in one extensive study; only kinetochore-negative micronuclei were found in another study. The formation of micronuclei was dependent on arachidonic acid supplementation. The micronuclei induced in the presence of a superoxide-generation system (hypoxanthine and xanthine oxidase) consisted exclusively of CREST-negative micronuclei and their formation was completely inhibited by pre-treatment with catalase. In addition, glutathione treatment inhibited both CREST-positive and negative micronuclei (Dobo & Eastmond, 1994).

In vitro in human cells, induction of DNA strand breaks was shown to be dependent on the presence of Cu(II). Hydroquinone induced sister chromatid exchanges and chromosomal aberrations without an exogenous metabolic system. The metabolic activation system was not required for the induction of micronuclei in human lymphocytes where kinetochore-positive micronuclei were found.

In vivo in mouse bone marrow, hydroquinone induced micronuclei and chromosomal aberrations in several studies but not sister chromatid exchanges in a single study. Hyperploidy and chromosome loss (as demonstrated by centromere-positive micronuclei) but not polyploidy were also found in mouse bone marrow. In mouse spermatocytes, chromosomal aberrations and hyperploidy were observed.

Hydroquinone inhibited intercellular communication in Chinese hamster cells *in vitro*. Topoisomerase II (Frantz *et al.*, 1996; Hutt & Kalf, 1996) but not topoisomerase I (Chen & Eastmond, 1995b) activity was inhibited *in vitro* by hydroquinone treatment.

Hydroquinone binding to calf thymus DNA and cysteine is enhanced by oxidation (prostaglandin H synthetase or cumene hydroperoxide) and inhibited by indomethacin

Table 1. Genetic and related effects of hydroquinone

Test system	Results [a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
PRB, SOS repair activity, *Salmonella typhimurium* TA1535/pSK1002, *umu* test	–	–	3300	Nakamura *et al*. (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	333	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	125	Sakai *et al*. (1985)
SA2, *Salmonella typhimurium* TA102, reverse mutation	+	NT	NG	Hakura *et al*. (1996)
SA4, *Salmonella typhimurium* TA104, reverse mutation	+	NT	25	Hakura *et al*. (1996)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	333	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	333	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	333	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	125	Sakai *et al*. (1985)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	125	Sakai *et al*. (1985)
SCG, *Saccharomyces cerevisiae* MP1, gene conversion	+	NT	1320	Fahrig (1984)
SCH, *Saccharomyces cerevisiae* MP1, homozygosis by mitotic recombination or gene conversion	–	NT	1320	Fahrig (1984)
SCF, *Saccharomyces cerevisiae* MP1, forward mutation	+	NT	1320	Fahrig (1984)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	?		28 000 ppm feed	Foureman *et al*. (1994)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	–		1500 ppm inj × 1	Foureman *et al*. (1994)
DIA, DNA single strand breaks, cross-links or related damage, LYS mouse lymphoma cells, alkaline elution *in vitro*	–	NT	11	Pellack-Walker & Blumer (1986)
DIA, DNA single strand breaks, isolated rat hepatocytes, alkaline elution *in vitro*	+	NT	33	Walles (1992)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitgro*	+	NT	2.5	McGregor *et al*. (1988a,b)
GIA, Gene mutation, Syrian hamster embryo cells, *hprt* locus *in vitro*	+	NT	1.1	Tsutsui *et al*. (1997)

Table 1 (contd)

Test system	Results [a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
GIA, Gene mutation, Syrian hamster embryo cells, ouabain resistance *in vitro*	+	NT	1.1	Tsutsui *et al*. (1997)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	+	0.5	Galloway *et al*. (1987)
SIS, Sister chromatid exchange, Syrian hamster embryo cells *in vitro*	+	NT	0.11	Tsutsui *et al*. (1997)
MIA, Micronucleus test, Chinese hamster embryonic lung CL-1 cells *in vitro*	+[c]	NT	1	Antoccia *et al*. (1991)
MIA, Micronucleus test, Chinese hamster lung V79 cells *in vitro*	(+)	NT	31.6	Seelbach *et al*. (1993)
MIA, Micronucleus test, Chinese hamster lung V79 cells *in vitro*	+	NT	2.8	Ellard & Parry (1993)
MIA, Micronucleus test, Chinese hamster XEM2 (V79 exp CYP1A1) cells *in vitro*	+	NT	2.8	Ellard & Parry (1993)
MIA, Micronucleus test, Chinese hamster SD1 (V79 exp CYP2B1) cells *in vitro*	+	NT	2.8	Ellard & Parry (1993)
MIA, Micronucleus test, Chinese hamster lung V79 cells *in vitro*	NT	+[d]	11.5	Dobo & Eastmond (1994)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	+	450	Galloway *et al*. (1987)
CIS, Chromosomal aberrations, Syrian hamster embryo cells *in vitro*	+	NT	3.3	Tsutsui *et al*. (1997)
AIA, Aneuploidy, DON:Wg3h Chinese hamster cells, dislocating metaphase chromosomes *in vitro*	+	NT	10	Warr *et al*. (1993)
AIA, Aneuploidy, LUC2 Chinese hamster cells, *in vitro*	–	NT	5	Warr *et al*. (1993)
AIA, Aneuploidy, Syrian hamster embryo cells *in vitro*	–	NT	3.3	Tsutsui *et al*. (1997)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay	+	NT	0.33	Tsutsui *et al*. (1997)
DIH, DNA strand breaks, cross-links or related damage, human lymphocytes, comet assay *in vitro*	?	+	11	Anderson *et al*. (1995)
DIH, DNA strand breaks, human promyelocytic HL60 cells, pulse field electrophoresis *in vitro*	+	NT	1.1	Hiraku & Kawanishi (1996)

Table 1 (contd)

Test system	Results [a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	4.4	Morimoto & Wolff (1980)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	+	110	Morimoto *et al*. (1983)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	6	Erexson *et al*. (1985)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	?[e]	NT	4.4	Knadle (1985)
MIH, Micronucleus test, human lymphocytes (kinetochore-positive) *in vitro*	+	NT	2.8	Yager *et al*. (1990)
MIH, Micronucleus test, human lymphocytes (kinetochore-positive) *in vitro*	+	NT	8.2	Robertson *et al*. (1991)
MIH, Micronucleus test, human lymphocytes *in vitro*	?	?	1	Van Hummelen & Kirsch-Volders (1992)
MIH, Micronucleus test, human lymphocytes *in vitro*	(+)[f]	NT	20	Ferguson *et al*. (1993)
MIH, Micronucleus test, human lymphocytes *in vitro*	–	+	50	Vian *et al*. (1995)
CHL, Chromosomal aberrations, human lymphocytes (fluorescence in-situ hybridization; FISH) *in vitro*	+	NT	11	Eastmond *et al*. (1994)
AIH, Aneuploidy, human lymphocytes *in vitro*, MN multicolour chromosome staining (FISH)	+	NT	8.3	Eastmond *et al*. (1994)
SVA, Sister chromatid exchange, (C57BL/Cnc × C3H/Cne)F_1 mouse bone marrow *in vivo*	–		120 ip × 1	Pacchierotti *et al*. (1991)
MVM, Micronucleus test, NMRI mouse bone marrow *in vivo*	+		50 sc × 6	Tunek *et al*. (1982)
MVM, Micronucleus test, Swiss CD-1 mouse bone marrow *in vivo*	+		80 ip × 1	Ciranni *et al*. (1988)
MVM, Micronucleus test, Swiss CD-1 mouse bone marrow *in vivo*	(+)		80 po × 1	Ciranni *et al*. (1988)
MVM, Micronucleus test, (101/E1 × C3H/E1)F_1 mouse bone marrow *in vivo*	+		50 ip × 1	Adler & Kliesch (1990)
MVM, Micronucleus test, (101/E1 × C3H/E1)F_1mouse bone marrow *in vivo*	+		15 ip × 3	Adler & Kliesch (1990)
MVM, Micronucleus test, Swiss CD-1 mouse bone marrow *in vivo*	(+)		60 ip × 1	Barale *et al*. (1990)
MVM, Micronucleus test, (102/E1 × C3H/E1)F_1 mouse bone marrow *in vivo*	+		50 ip × 1	Adler *et al*. (1991)
MVM, Micronucleus test, (102/E1 × C3H/E1)F_1 mouse bone marrow *in vivo*	+[c]		100 ip × 1	Miller *et al*. (1991)

Table 1 (contd)

Test system	Results [a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
MVM, Micronucleus test, (C57BL/Cnc × C3H/Cne)F_1 mouse bone marrow *in vivo*	+		40 ip × 1	Pacchierotti *et al*. (1991)
MVM, Micronucleus test, Swiss CD-1 mouse bone marrow *in vivo*	+		20 ip × 1	Marrazinni *et al*. (1994a)
MVM, Micronucleus test, Swiss CD-1 mouse bone marrow *in vivo*	+		80 ip × 1	Marrazinni *et al*. (1994b)
MVM, Micronucleus test, CD-1 mouse bone marrow *in vivo*	+		60 ip × 3	Chen & Eastmond (1995a)
CBA, Chromosomal aberrations, (102/E1 × C3H/E1)F_1 mouse bone marrow *in vivo*	+		75 ip × 1	Xu & Adler (1990)
CBA, Chromosomal aberrations, Swiss CD-1 mouse bone marrow *in vivo*	+		80 ip × 1	Marrazinni *et al*. (1994b)
CCC, Chromosomal aberrations, (102/E1 × C3H/E1)F_1 mouse spermatocytes treated *in vivo*	+		40 ip × 1	Ciranni & Adler (1991)
CGG, Chromosomal aberrations, (102/E1 × C3H/E1)F_1 mouse spermatogonia treated *in vivo*	+		40 ip × 1	Ciranni & Adler (1991)
AVA, Aneuploidy, (102/E1 × C3H/E1)F_1 mouse bone marrow polyploidy *in vivo*	–		100 ip × 1	Xu & Adler (1990)
AVA, Aneuploidy, (C57BL/Cnc × C3H/Cne)F_1 mouse bone marrow hyperploidy *in vivo*	+		80 ip × 1	Pacchierotti *et al*. (1991)
AVA, Aneuploidy, (C57BL/Cnc × C3H/Cne)F_1 mouse bone marrow polyploidy *in vivo*	–		120 ip × 1	Pacchierotti *et al*. (1991)
AVA, Aneuploidy, (C57BL/Cnc × C3H/Cne)F_1 mouse spermatocytes hyperploidy *in vivo*	+		80 ip × 1	Leopardi *et al*. (1993)
AVA, Aneuploidy, Swiss CD-1 mouse bone marrow polyploidy *in vivo*	–		80 ip × 1	Marrazinni *et al*. (1994b)
AVA, Aneuploidy, Swiss CD-1 mouse bone marrow hyperploidy *in vivo*	+		80 ip × 1	Marrazinni *et al*. (1994b)

Table 1 (contd)

Test system	Results [a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
AVA, Aneuploidy, CD-1 mouse bone marrow *in vivo*, MN multicolour chromosome staining (FISH)	+		60 ip × 3	Chen & Eastmond (1995a)
BID, Binding (covalent) to DNA, mouse P388D_1 cells *in vitro*	+	NT	5.5	Kalf *et al*. (1990)
BID, Binding (covalent) to calf thymus DNA *in vitro*	+	NT	5.5	Leanderson & Tagesson (1990)
BID, Binding (covalent) to DNA, cultured rat Zymbal glands *in vitro*	+	NT	750	Reddy *et al*. (1990)
BID, Binding (covalent) to calf thymus DNA *in vitro*	–	+[g]	11	Schlosser *et al*. (1990)
BID, Binding (covalent) to DNA, human promyelocytic HL-60 cells *in vitro*	+	NT	5.5	Lévay *et al*. (1991)
BID, Binding (covalent) to DNA, male B6C3F_1 mouse bone-marrow cells *in vitro*	+	NT	11	Lévay *et al*. (1993)
BID, Binding (covalent) to DNA, human bone-marrow macrophages *in vitro*	+	NT	11	Lévay *et al*. (1993)
BID, Binding (covalent) to DNA, human promyelocytic HL-60 cells *in vitro*	+	NT	27.5	Pathak *et al*. (1995)
BID, Binding (covalent) to DNA, B6C3F_1 mouse bone marrow *in vitro*	+	NT	27.5	Pathak *et al*. (1995)
BID, Binding (covalent) to DNA, human promyelocytic HL-60 cells *in vitro*	+	NT	5.5	Lévay & Bodell (1996)
BVD, Binding (covalent) to DNA, Sprague-Dawley rat Zymbal gland, liver or spleen *in vivo*	–		150 po × 4	Reddy *et al*. (1990)
BVD, Binding (covalent) to DNA, Fischer 344 rat kidneys *in vivo*	–		50 po, 5 d/wk, 6 wk	English *et al*. (1994b)
ICR, Inhibition of intercellular communication, V79MZ Chinese hamster cells *in vitro*	+	NT	0.055	Vang *et al*. (1993)

Table 1 (contd)

Test system	Results [a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
DNA single-strand breaks on supercoiled Bluescript plasmid DNA	–	+	11	Schlosser *et al*. (1990)
Binding (covalent) to porcine brain tubulin [porcine brain tubulin assembly assay] *in vitro*	–	NT	2750	Brunner *et al*. (1991)
Inhibition of assembly of bovine microtubules *in vitro*	(+)	NT	110	Wallin & Hartley-Hasp (1993)

[a] +, positive; (+), weakly positive; –, negative; NT, not tested; ?, inconclusive
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; po, oral; NG, not given; inj, injection; ip, intraperitoneal; sc, subcutaneous
[c] No increase in % kinetochore-positive micronuclei compared with controls
[d] Supplemented with arachidonic acid; increase in both kinetochore-positive and –negative micronucleated cells compared with controls (CREST-labelling procedure)
[e] Positive if glutathione depleted with diethyl maleate
[f] Size ratio of micronuclei to nucleus is not significant different from controls.
[g] With prostaglandin H synthetase for oxidation

(Kalf *et al*., 1990; Schlosser *et al*., 1990). Hydroquinone bound weakly to isolated bovine microtubules but not to porcine brain tubulin *in vitro* and to DNA in most of the in-vitro studies, in single studies with rat Zymbal glands in culture and in mice bone marrow *in vitro*. *In vivo*, hydroquinone did not bind to DNA from Zymbal gland, liver, spleen or kidneys of rat treated orally; it did not induce DNA strand breaks in plasmid DNA.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to hydroquinone may occur during its production, its use as an inhibitor, antioxidant and intermediate in the production of dyes, paints, motor fuels and oils, and in black-and-white photographic processing. Hydroquinone occurs naturally in certain plant species. It is used as a topical treatment for skin hyperpigmentation.

5.2 Human carcinogenicity data

A cohort of workers with definite and lengthy exposure to hydroquinone had low cancer rates compared with two comparison populations; the reason for the lower than expected rates is unclear. A cohort of lithographers, some of whom had worked with hydroquinone, had an excess of malignant melanoma based on five cases; only two of the cases had reported exposure to hydroquinone.

5.3 Animal carcinogenicity data

Hydroquinone was tested for carcinogenicity in two studies in mice and two studies in rats by oral administration. It was also tested in rats for promoting activity in assays for bladder, stomach, liver, lung, oesophagus and kidney carcinogenesis and in one study in hamsters for pancreatic carcinogenesis.

In mice, hydroquinone induced hepatocellular adenomas in females in one study and in males in another study. In rats it induced renal tubule adenomas in males in two studies.

Hydroquinone had no promoting activity in most assays; an increase in the multiplicity of oesophageal tumours was observed in one study and in the multiplicity of renal cell tumours in another study. No promoting effect on pancreatic carcinogenesis was observed in the study in hamsters.

5.4 Other relevant data

Hydroquinone is metabolized mainly to conjugates, but a small percentage may be converted to 1,4-benzoquinone, conjugated with glutathione or form DNA adducts *in vitro*.

It caused toxicity in several organs, notably the kidney and forestomach.

Hydroquinone was mutagenic in many in-vitro systems using a variety of end-points. Also, after intraperitoneal administration, it caused genotoxicity or chromosomal aberrations in bone marrow.

5.5 Evaluation

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

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

Overall evaluation

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

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