CATECHOL

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

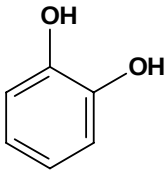
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 120-80-9
Chem. Abstr. Name: 1,2-Benzenediol
IUPAC Systematic Name: Pyrocatechol
Synonyms: Catechin; 1,2-dihydroxybenzene

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*: Colourless monoclinic crystals (Budavari, 1996)
(*b*) *Boiling-point*: 245°C (Lide, 1997)
(*c*) *Melting-point*: 105°C (Lide, 1997)
(*d*) *Solubility:* Very soluble in water, benzene, chloroform, diethyl ether, ethanol, pyridine and aqueous alkalis (Budavari, 1996; Lide, 1997)
(*e*) *Vapour pressure*: 4 Pa at 20°C; relative vapour density (air = 1), 3.79 (Verschueren, 1996; United States National Library of Medicine, 1997)
(*f*) *Flash-point:* 127.2°C, open cup (American Conference of Governmental Industrial Hygienists, 1991)
(*g*) *Conversion factor*: $mg/m^3 = 4.5 \times ppm$

1.2 Production and use

Worldwide consumption of catechol in 1980 was estimated to be about 20 thousand tonnes. Catechol is currently produced in France, Italy, Japan, the United Kingdom and the United States (Hamamoto & Umemura, 1991; Krumenacker *et al.*, 1995).

Approximately 50% is used as starting material for insecticides, 35–40% for perfumes and drugs and 10–15% for polymerization inhibitors and other chemicals. Catechol has also been used as an antiseptic, in photography, dyestuffs, electroplating, specialty inks, antioxidants and light stabilizers, and in organic synthesis (Hamamoto & Umemura, 1991; Lewis, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), approximately 14 000 workers in the United States were potentially exposed to catechol (see General Remarks). Occupational exposures to catechol may occur in its production, in the production of insecticides, perfumes and drugs, in metal-plating shops and in coal-processing.

1.3.2 *Environmental occurrence*

Catechol occurs naturally in fruits and vegetables such as onions, apples and crude beet sugar, and in trees such as pine, oak and willow. Catechol may be released to the environment during its manufacture and use. It has been detected at low levels in ambient and urban air, groundwater, drinking-water and soil samples. It has been found in wastewaters from coal conversion, coal-tar chemical production and bituminous shale (United States National Library of Medicine, 1997). It is present in cigarette smoke at 100–360 μg per cigarette (IARC, 1986).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 23 mg/m^3 as the 8-h time-weighted average threshold limit value, with a skin notation, for occupational exposures to catechol in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

No international guideline for catechol in drinking-water has 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

In skin painting studies in mice, catechol increased the carcinogenic effects of benzo[*a*]pyrene on the skin (IARC, 1977).

3.1 Oral administration

3.1.1 *Mouse*

Groups of 30 male and 30 female B6C3F_1 mice, six weeks of age, were administered catechol (> 99% pure) at 0 or 0.8% in the diet for 96 weeks. Catechol reduced the body weight gain of both males and females but did not affect survival. In exposed mice, the incidence of forestomach hyperplasia (16/30 males, 25/29 females) was increased. Forestomach papillomas occurred in one male and one female compared with none in controls. In the glandular stomach, 29/30 males and 21/29 females exhibited adenomatous hyperplasia, but no adenocarcinomas. No increase in the incidence of other neoplasms was observed (Hirose *et al*., 1990, 1993a).

3.1.2 *Rat*

Two groups of 30 male Fischer rats, eight weeks of age, were administered catechol (purity, > 99%) at 0 or 0.5% in the drinking-water for 78 weeks. Catechol alone did not increase the incidence of any tumour type (La Voie *et al*., 1985). [The Working Group noted the short duration of the study.]

Groups of 30 male MRC-Wistar rats, six weeks of age, were administered catechol (purity, > 99%) at concentrations of 0 or 2 mg/kg in the diet for up to 15 months. Catechol alone induced no increase in neoplasms (Mirvish *et al*., 1985). [The Working Group noted the short duration of the study.]

Groups of 30 male and 30 female Fischer 344 rats, six weeks of age, were administered catechol (> 99% pure) at 0 or 0.8% in the diet for 104 weeks. Catechol reduced the body weight gain of both males and females and increased the liver weight of males but did not affect survival. In exposed rats, forestomach hyperplasia was increased in both sexes (24/28 males, 23/28 females) and papillomas occurred in 2/24 (7%) males, compared with none in controls. In the glandular stomach, 100% of exposed males and females exhibited adenomatous hyperplasia and adenocarcinomas occurred in 15/28 males and 12/28 females ($p < 0.001$) compared with none in controls. No change in the incidence of other neoplasms was observed (Hirose *et al*., 1990, 1993a).

Groups of 20 or 30 male Wistar (Crj:Wistar), WKY (WKY/NCrj), Lewis (LEW/Crj) and SD (Crj:CD) rats, six weeks of age, were administered catechol (> 99% pure) in the diet at 0 or 0.8% for 104 weeks. Weight gain was reduced in all exposed groups but no effect on survival was observed. In the forestomach, the incidence of hyperplasia was significantly increased in exposed Wistar, WKY and SD rats compared with controls. Papillomas occurred in 6/30 SD rats ($p < 0.05$), 2/30 Wistar rats and 1/30 WKY rats and carcinomas in 1/30 SD and 1/30 Wistar rats compared with none in controls. In the

glandular stomach, all strains developed 97–100% incidence of adenomas compared with none in controls and adenocarcinomas occurred in 23/30 ($p < 0.01$) SD, 22/30 ($p < 0.01$) Lewis, 20/30 ($p < 0.01$) Wistar and 3/30 ($p > 0.05$) WKY rats compared with none in controls. No increase in any other tumour type was found in exposed WKY rats, while pituitary adenomas/carcinomas were decreased in exposed Wistar rats (4/30 versus 8/20 controls; $p < 0.05$) and SD rats (6/30 versus 11/21 controls; $p < 0.05$) and pituitary adenomas in Lewis rats (2/30 versus 14/20 controls; $p < 0.01$). In Wistar rats, islet-cell adenomas/carcinomas were also decreased (0/30 versus 5/20 controls; $p < 0.01$) (Tanaka *et al*., 1995).

3.2 Skin application

Mouse: Groups of 30 female SEN mice, six weeks of age, were administered catechol (purified by recrystallization) at 0 or 2000 μg/animal topically three times per week for 490–560 days. Catechol alone induced no skin tumours and none occurred in a total of 125 control mice (Van Duuren *et al*., 1986).

Groups of 30 female Crl:DC-1(1CR) BR mice, seven weeks of age, were administered catechol [purity unspecified] topically five times per week for 48 weeks at a dose of 0 or 250 μg per animal. Catechol alone induced no skin tumours. In a second experiment, groups of 30 mice were administered acetone or 500 μg catechol per animal 10 times every other day and, 10 days after the last exposure, 12-*O*-tetradecanoylphorbol 13-acetate (TPA) was applied as a promoter for 20 weeks. In mice given catechol before promotion, 5/29 developed skin tumours [unspecified] compared with 3/29 mice given acetone plus TPA (Melikian *et al*., 1989).

3.3 Administration with known carcinogens

3.3.1 *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. Catechol [purity unspecified] was administered at concentrations of 0 or 0.8% in the diet for 22 weeks and all animals were killed at week 24. When catechol was administered after initiation, no increase in bladder tumours was produced (Miyata *et al*., 1985).

Groups of 10–20 male Fischer 344 rats, seven weeks of age, received catechol (> 99.8% pure) in the diet at concentrations of 0 or 1.5% for four weeks followed by 0.8% for 47 weeks either with no other exposure or one week after exposure to *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine to initiate stomach carcinogenesis. With catechol alone, the incidence of forestomach papillomas was 1/15 compared with 0/10 in untreated controls. Glandular stomach adenocarcinomas were found in 3/15 rats compared with 0/10 in controls. Catechol increased the incidence of squamous-cell carcinomas of the forestomach induced by the initiator from 5/19 to 19/19 ($p < 0.001$). In the glandular stomach, the incidence of adenocarcinomas in the pyloric region was 18/19 ($p < 0.001$) compared with none in rats given only the initiator (Hirose *et al*., 1987).

Groups of 7–10 male Sprague-Dawley rats, weighing 200 g, were administered catechol (purity, > 98%) at concentrations of 0 or 100 mg/kg in the diet for six weeks beginning one week after partial hepatectomy and intraperitoneal injection of 30 mg/kg bw *N*-nitrosodiethylamine to initiate liver carcinogenesis. Catechol after initiation did not increase the multiplicity of liver enzyme-altered (γ-glutamyltranspeptidase) foci (Stenius *et al*., 1989).

Groups of 11–14 male Fischer 344 rats, five weeks of age, were administered catechol (< 99% pure) at 0 or 0.8% alone for 52 weeks or after exposure to six intraperitoneal injections of 25 mg/kg bw *N*-nitrosomethyl-*n*-amylamine to initiate upper digestive tract carcinogenesis. Catechol given after carcinogen increased the incidence of papillomas of the tongue from 1/11 in rats given carcinogen alone to 8/14 ($p < 0.02$) and carcinomas of the oesophagus from 0/11 in controls to 9/14 ($p < 0.001$) (Yamaguchi *et al*., 1989).

Groups of 10 or 19 male Fischer 344 rats, six weeks of age, were administered catechol (purity, > 98%) in the diet at 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. Catechol did not affect body weight or bladder weight, but when given after initiator, it reduced final body weight, but did not affect bladder weight. Catechol did not induce bladder lesions. Feeding of catechol after the initiator did not increase the incidence or multiplicity of bladder neoplasms induced by initiation alone (Kurata *et al*., 1990).

Groups of 5–30 male Fischer 344/DuCrj rats, nine weeks of age, were administered catechol [purity unspecified] at a concentration of 0.8% in the diet for 16 weeks either alone or after a single intraperitoneal injection of 100 mg/kg bw *N*-nitrosodiethylamine, 20 mg/kg bw *N*-methyl-*N*-nitrosourea (four times) and 0.1% *N*-nitroso-*N*-bis(2-hydroxypropyl)amine in the drinking-water during weeks 3–4. Catechol alone induced low incidences of hyperplasia of the forestomach and hyperplasia and adenoma of the glandular stomach. The incidence of forestomach papillomas in rats given carcinogens was 0%, whereas in rats treated with carcinogens and catechol, the incidence of forestomach papillomas was 35% and forestomach carcinomas occurred in 5% [no numerical values given]. Catechol did not affect the incidence of oesophageal, thyroid or bladder tumours (Fukushima *et al*., 1991).

Groups of 15 or 20 male Fischer 344/DuCrj rats, six weeks of age, were given a single intraperitoneal injection of 100 mg/kg bw *N*-nitrosodiethylamine, followed by four injections of 20 mg/kg bw *N*-methyl-*N*-nitrosourea during weeks 1 and 2, then four subcutaneous injections of 40 mg/kg bw 1,2-dimethylhydrazine and 0.05% *N*-nitrosobutyl-*N*-(4-hydroxybutyl)amine and 0.1% *N*-nitroso-*N*-bis(2-hydroxypropyl)amine in the drinking-water during weeks 3 and 4, to initiate carcinogenesis in multiple organs. Rats were then fed with diet containing 0.8% catechol [purity unspecified] for the next 24 weeks or for 100 weeks. Rats given catechol for only 24 weeks were either killed at the end of this time or were maintained thereafter on basal diet. A control group was given the multiple initiation treatments only. Catechol given for 24 weeks after initiation

reduced body weight gain compared to initiation alone. After 24 weeks of exposure, catechol induced combined forestomach papillomas and carcinomas in 10/13 ($p < 0.01$) and glandular stomach adenomas in 11/13 ($p < 0.01$) compared with none in rats given initiators alone. In the group given catechol for 24 weeks after initiation and then maintained on basal diet, all rats were dead by 64 weeks versus 72 weeks for those given only initiation. In this group, no increase in cancer was observed. In the group given continuous catechol administration after initiation, all rats were dead at 56 weeks versus 72 weeks with only initiation. Catechol exposure increased the incidence of combined forestomach squamous-cell papilloma and carcinoma to 18/19 ($p < 0.01$) compared with 9/20 with initiation, and the incidence of glandular stomach adenoma to 9/19 ($p < 0.01$) compared with 1/20 (Hagiwara *et al*., 1993).

Groups of 10 or 15 male Fischer 344 rats, six weeks of age, were administered catechol (> 98% pure) in the diet at concentrations of 0 or 0.8% either alone or after exposure to a standard protocol of treatment with *N*-nitrosodiethylamine, *N*-methyl-*N*-nitrosourea, 1,2-dimethylhydrazine, *N*-nitrosobutyl-*N*-(4-hydroxybutyl)amine and *N*-nitroso-*N*-bis(2-hydroxypropyl)amine to initiate carcinogenesis in multiple organs. Catechol alone or after initiation reduced weight gain and induced mild hyperplasia in the forestomach and adenomas in the glandular stomach in 10/10 rats ($p < 0.001$) compared with 0/10 in unexposed controls. In initiated rats, catechol produced carcinoma *in situ* or squamous carcinoma in 6/15 rats ($p < 0.05$) compared with 0/14 rats given the initiators only. It also increased the incidence of glandular stomach adenomas and carcinomas to 4/15 ($p < 0.05$) versus 0/14 rats subjected to initiation only (Hirose *et al*., 1993b).

Groups of 20 male Wistar/Crj rats, six weeks of age, were administered catechol [purity unspecified] in the diet at a concentration of 0.8% for 36 weeks either alone or starting one week after exposure to 0.1% *N*-nitrosoethyl-*N*-(hydroxyethyl)amine in the drinking-water for three weeks to initiate liver and kidney carcinogenesis. The final body weights of rats given catechol were lower than those of rats given either basal diet or initiator. Catechol alone did not affect liver weights but increased relative kidney weights. When catechol was given after the initiator, there was no effect on liver or kidney weights. Catechol did not enhance the incidence of preneoplastic or neoplastic lesions in the liver or kidneys (Okazaki *et al*., 1993).

Groups of 20 male Fischer 344 rats, five weeks of age, were administered catechol (purity, > 99%) at concentrations 0 or 0.8% in the diet for 52 weeks alone or beginning one week after a single intragastric instillation of 150 mg/kg bw *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine to initiate stomach carcinogenesis. Catechol alone induced no neoplasms, but increased the incidence of forestomach hyperplasia compared with that in unexposed rats. In initiated rats, catechol exposure led to forestomach squamous-cell carcinoma in 17/20 ($p < 0.01$) compared with 6/18 in rats without catechol. In the glandular stomach, catechol after initiation induced adenocarcinomas in 15/20 ($p < 0.01$) rats compared with 0/18 rats receiving initiation treatment alone (Kawabe *et al*., 1994).

3.3.2 *Hamster*

Groups of Syrian golden hamsters, six weeks of age, were exposed to catechol (purity, > 98%) at concentrations of 0 or 1.5% in the diet for 16 weeks either alone (10 and 15 hamsters, respectively) or after two subcutaneous injections of 70 mg/kg bw *N*-nitroso-bis(2-oxopropyl)amine (20 hamsters) to initiate pancreatic carcinogenesis. Catechol alone did not affect body weights or pancreas weights compared with untreated controls, but reduced relative liver weight. Given after initiator, it did not affect body weight or pancreas weight, but reduced liver weight compared with hamsters given initiator. All animals were killed at 20 weeks. Catechol alone did not induce neoplastic lesions in pancreas or liver lesions. In hamsters given catechol after initiator, no increase in pancreatic lesions was found. In the forestomach and glandular stomach of hamsters given catechol, a higher frequency of epithelial hyperplasias was observed than in control groups [numerical data not provided] (Maruyama *et al*., 1991). Similarly, no enhancement of pancreatic carcinogenesis was observed in a later study using *N*-nitroso-*N*-bis(2-hydroxypropyl)amine as an initiator of pancreatic carcinogenesis (Maruyama *et al*., 1994).

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

4.1 Absorption, distribution, excretion and metabolism

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

Proposed metabolic pathways of catechol are summarized in Figure 1. The major metabolic pathways in experimental animals are sulfation and glucuronidation.

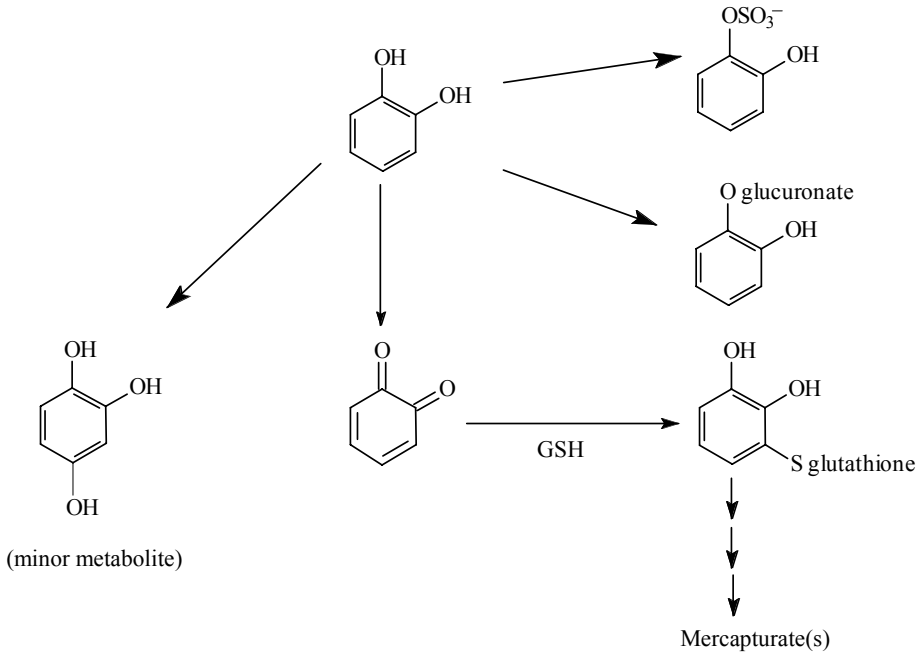
Catechol may be oxidized by peroxidases to the reactive intermediate benzo-1,2-quinone, which readily binds to proteins (Bhat *et al*., 1988); this process, catalysed by rat or human bone-marrow cells in the presence of H_2O_2 (0.1 mM), is stimulated by phenol (0.1–10 mM), and decreased by hydroquinone and by glutathione, which conjugates with benzo-1,2-quinone. These phenols (phenol, catechol and hydroquinone) may play a role in benzene toxicity to bone marrow: all three are formed as benzene metabolites (Smith *et al*., 1989) and they interact in several ways as far as their bioactivation by (myelo)peroxidases is concerned (Smith *et al*., 1989; Subrahmanyam *et al*., 1990).

4.2 Toxic effects

4.2.1 *Humans*

It was noted previously that skin contact with catechol causes dermatitis, and absorption through the skin may give rise to symptoms similar to those seen in phenol poisoning (IARC, 1977).

Figure 1. Metabolism of catechol



4.2.2 *Experimental systems*

Administration of catechol (1.5% in the diet) for 20 weeks induced mild to moderate hyperplasia but no papillomatous lesions in the forestomach in Syrian hamsters. Labelling index, after an intraperitoneal dose of [^{3}H]thymidine, was elevated in the pyloric region, but not in the forestomach or urinary bladder (Hirose *et al*., 1986).

In male Fischer rats, oral administration of catechol for four or eight weeks (0.8% in the diet) caused hyperplasia in the forestomach epithelium (4/5 rats) and increased DNA synthesis, as measured by a BrdU-labelling index, from 6.3% in controls to 16.8% ($p < 0.01$) after eight weeks (Shibata *et al*., 1990a,b). In pyloric mucosa of Fischer 344 rats given dietary catechol (0.8%) for four weeks, cell proliferation was observed (cells/pit column: control, 20.8; treated, 35.5; $p < 0.05$), accompanied by submucosal cell growth and an increase in DNA synthesis from 5.0% in controls to 10.3% ($p < 0.05$) (Ohgaki *et al*., 1989). The pyloric mucosa of Fischer 344 rats given dietary catechol (0.8%) for eight weeks also showed an increase in pepsinogen-altered preneoplastic foci from 0.2/100 pyloric glands in controls to 3.6/100 pyloric glands ($p < 0.05$) and an increased DNA labelling index from 12.4% in controls to 20.6% ($p < 0.01$) (Shibata *et al*., 1990a,b). After 60 weeks of dietary administration of 0.8% catechol to WKY/Ncrj rats, adenomatous hyperplasia and Pg1-altered foci were observed. The CCGG sites but not CGCG sites of the *Pg1* gene showed slightly increased methylation frequency in adenomatous tissues, while the methylation pattern of the *Pg1* gene was not significantly different from that of normal tissue in the Pg1-altered foci (Tatematsu *et al*., 1993). After

dietary administration of 0.8% catechol to Fischer 344 rats for 12, 24, 48 or 72 weeks and recovery on basal diet for 84, 72, 48 or 24 weeks, respectively, mucosal thickness and DNA labelling indices in the glandular stomach were significantly reduced in comparison with the values from catechol-fed rats that were not permitted a recovery period (Hirose *et al*., 1992).

Catechol (approx. 10^{-5} mol/L) inhibited the growth of bone-marrow cells from female C57BL/6 × DBA/2 mice (Seidel *et al*., 1991) and from male C57 and SW mice (Neun *et al*., 1992). Catechol (25, 50, 75 or 100 mg/kg bw, single intraperitoneal administration) decreased the incorporation of ^{59}Fe to erythrocytes in a dose-dependent fashion in female Swiss mice, when administered with phenol (50 mg/kg bw, single intraperitoneal administration) (Snyder *et al*., 1989). Catechol induced apoptosis in the human leukaemia cell line HL60 at concentrations (50 μmol/L) at which necrosis was not observed (Moran *et al*., 1996). On the other hand, catechol (≥ 0.5 μmol/L) prevented elimination by apoptosis of G418-resistant, transformed Swiss 3T3 M × Cl1 cells by co-cultured TGF-β-treated C3H 10T½ cells (Schaeffer *et al*., 1995).

A high concentration (0.5 mmol/L) of catechol induced a small-scale cytosol-to-membrane transport of protein kinase C, followed by inactivation of the enzyme activity, in cultured LL/2 lung carcinoma cells (Gopalakrishna *et al*., 1994).

In a study on the immunotoxic effects of cigarette tar components, it was shown that catechol 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 lymphoblasts (Li *et al*., 1997). Catechol did not inhibit Fc-receptor-mediated phagocytosis in mouse peritoneal macrophages at the highest concentrations tested (0.1 mmol/L) (Manning *et al*., 1994). Catechol (≤ 10 mmol/L) had no effect on the colony formation of granulocytes/macrophages induced by a recombinant granulocyte/macrophage colony-stimulating factor of murine bone-marrow cells (Irons *et al*., 1992).

Catechol (100 mg/kg bw, a single oral dose) given to male Sprague-Dawley rats did not affect the urinary excretion of malonaldehyde but did increase hepatic ornithine decarboxylase activity from a control level of 15.5 pmol/mg/h to 99.3 pmol/mg/h and, *in vitro*, 0.3 mmol/L induced rapid depletion of the glutathione content of isolated hepatocytes (Stenius *et al*., 1989). Addition of 0.25 mM catechol to HL-60 cells increased endogenous hydrogen peroxide levels three-fold, but 0.25 mM hydroquinone had no effect upon resting levels, whereas 0.25 mM catechol + 0.05 mM hydroquinone provoked a five-fold increase in endogenous hydrogen peroxide (Lévay & Bodell, 1996).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Catechol had no adverse effects upon cultured 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)

Catechol did not induce gene mutations in *Salmonella typhimurium* or DNA repair in a mouse host-mediated assay in *Escherichia coli.*

In studies with eukaryotic cell in-vitro assays, most experiments were performed in the absence of an exogenous metabolic activation system, and almost all results indicated genetic toxicity. In a single study with the yeast *Saccharomyces cerevisiae*, catechol induced forward mutation but not gene conversion or homozygosis. When incubated with cultured non-human mammalian cells, catechol induced DNA strand breaks in two studies (which included one with rat primary hepatocytes), gene mutations (three studies) and sister chromatid exchanges, chromosomal aberrations, aneuploidy and cell transformation (all within the same study). Another cell transformation assay with BALB/3T3 cells showed no response at relative cloning efficiencies lower than 27%. Inhibition of gap-junctional intercellular communication was also demonstrated in one study. Mutagenic activity at the *tk* locus of mouse lymphoma cells was blocked by superoxide dismutase (McGregor *et al*., 1988). In cultured human lymphocytes, catechol induced DNA strand breaks (one study) and sister chromatid exchanges (three studies). Also in human lymphocytes, micronuclei and chromosome loss (as indicated by kinetochore staining) were induced by catechol co-incubated with hydroquinone, but not in the absence of hydroquinone. Two- to three-fold increases in total micronuclei were observed at doses down to 0.5 μM, but with no response increasing with dose (Yager *et al.*, 1990). Perhaps of relevance to some of these in-vitro effects, catechol (1 mM) did not inhibit topoisomerase I activity, whereas topoisomerase II was inhibited by the same concentration (but not by 0.5 mM) and even by 0.01 mM in the presence of horseradish peroxidase (Chen & Eastmond, 1995; Franz *et al*., 1996).

In single in-vivo studies, catechol did not induce DNA strand breaks or somatic cell mutations in the mouse spot test (one study). On the other hand, micronuclei were induced in mouse bone marrow (three of four studies). In one of these positive micronucleus test studies, the effect was greater after intraperitoneal injection than after gavage administration, while, in the other positive study, the effect of an intraperitoneal injection was enhanced by either phenol or hydroquinone.

Adducts

Catechol added to HL-60 cells or administered intraperitoneally at 75 mg/kg bw to $B6C3F_1$ mice, from which bone-marrow cells were sampled, did not induce formation of 8-hydroxydeoxyguanosine, as might be expected if there had been oxidative damage to DNA. When catechol was administered with hydroquinone, however, an increase in 8-hydroxydeoxyguanosine was observed (Kolachana *et al*., 1993). Leanderson and Tagesson (1990) found no covalent binding of catechol to DNA *in vitro*. Using a ^{32}P-postlabelling

Table 1. Genetic and related effects of catechol

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, SOS induction, *Salmonella typhimurium*/pSK1002, *umu* test	–	–	3300	Nakamura *et al*. (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	NT	500	Nazar *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1667	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000	Yoshida & Fukuhara (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1667	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1667	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	Yoshida & Fukuhara (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1667	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	Yoshida & Fukuhara (1983)
SCG, *Saccharomyces cerevisiae* MP1, gene conversion	–	NT	2500	Fahrig (1984)
SCH, *Saccharomyces cerevisiae* MP1, homozygosis	–	NT	2500	Fahrig (1984)
SCF, *Saccharomyces cerevisiae* MP1, forward mutation	+	NT	2500	Fahrig (1984)
DIA, DNA strand breaks/alkali-labile sites, rat primary hepatocytes *in vitro*	(+)	NT	330	Solveig Walles (1992)
DIA, DNA strand breaks, mouse lymphoma L5178YS cells *in vitro*	–	NT	110	Pellack-Walker & Blumer (1986)
DIA, DNA strand breaks/cross-links, mouse lymphoma cells *in vitro*	+	+	55	Garberg *et al*. (1988)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	2.5	McGregor *et al*. (1988)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	1.14	Wangenheim & Bolcsfoldi (1988)
GIA, Gene mutation, Syrian hamster embryo cells, *hprt* locus *in vitro*	+	NT	0.33	Tsutsui *et al*. (1997)
GIA, Gene mutation, Syrian hamster embryo cells, Na^+/K^+ ATPase locus *in vitro*	+	NT	1.1	Tsutsui *et al*. (1997)
SIS, Sister chromatid exchange, Syrian hamster embryo cells *in vitro*	+	NT	1.1	Tsutsui *et al*. (1997)
CIS, Chromosomal aberrations, Syrian hamster embryo cells *in vitro*	+	NT	0.33	Tsutsui *et al*. (1997)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
AIA, Aneuploidy, Syrian hamster embryo cells *in vitro*	+	NT	3.3	Tsutsui *et al*. (1997)
TBM, Cell transformation, BALB/3T3 mouse cells, focus assay	–	NT	2	Atchison *et al*. (1982)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay	+	NT	0.11	Tsutsui *et al*. (1997)
DIH, DNA strand breaks/alkali-labile sites, human lymphocytes, comet assay *in vitro*	(+)[c]	+	11	Anderson *et al*. (1995)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	4	Morimoto & Wolff (1980)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	33	Morimoto (1983)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	6	Erexson *et al*. (1985)
MIH, Micronucleus test, human lymphocytes *in vitro*	+[c]	NT	22	Yager *et al*. (1990)
MIH, Micronucleus test, human lymphocytes *in vitro*	–	NT	8.3	Robertson *et al.* (1991)
HMM, Host-mediated assay, *Escherichia coli* K-12 *uvr B/rec A* DNA repair in blood, liver, lungs, kidneys, testicles of male NMRI mice	–		200 po × 1	Hellmér & Bolcsfoldi (1992)
DVA, DNA strand breaks/cross-links, Fischer 344 rats *in vivo*	–		90 po × 1	Furihata *et al*. (1989)
MST, Mouse spot test, C579BL × T mouse embryos	–		22 ip × 1	Fahrig (1984)
MVM, Micronucleus test, male NMRI mouse bone marrow *in vivo*	–		42 sc × 6	Tunek *et al*. (1982)
MVM, Micronucleus test, male CD-1 mouse bone marrow *in vivo*	+		40 po × 1	Ciranni *et al*. (1988a)
MVM, Micronucleus test, pregnant female CD-1 mouse bone marrow and fetal liver *in vivo*	+		40 po × 1	Ciranni *et al*. (1988b)
MVM, Micronucleus test, CD-1 mouse bone marrow *in vivo*	+		10 ip × 1	Marrazzini *et al*. (1994)
ICR, Inhibition of cell communication, Chinese hamster lung V79 cells	+	NT	0.25	Bohrman *et al*. (1988b)

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

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw/day; po, oral; ip, intraperitoneal; sc, subcutaneous

[c] Higher percentage stained kinetochore-positive compared to controls

technique, Lévay and Bodell (1996) found that treatment of HL-60 cells with 0.5 mM catechol for 24 h resulted in a relative adduct level of 0.21×10^{-7}. Addition of 0.05–0.25 mM hydrogen peroxide increased the relative adduct level to $0.83–2.10 \times 10^{-7}$, whereas co-administration of hydrogen peroxide with 1,2,4-benzenetriol had no additional effect.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to catechol may occur in its production, in the production of insecticides, perfumes and drugs, in metal plating and in coal processing. Catechol occurs naturally in fruits and vegetables. It is present in cigarette smoke and has been detected at low levels in ambient air and water.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Catechol was tested for carcinogenicity by oral administration in one study in mice and in two studies in rats. No increase in the incidence of malignant tumours was found in mice. In rats, it induced adenocarcinomas in the glandular stomach in several strains. In one study in mice by skin application, no skin tumour was observed. In several experiments in rats involving administration with known carcinogens, catechol enhanced the incidence of papillomas of the tongue, carcinomas of the oesophagus, squamous-cell carcinomas of the forestomach and adenocarcinomas of the glandular stomach.

5.4 Other relevant data

Catechol is oxidized by peroxidases to the reactive intermediate benzo-1,2-quinone, which binds to protein. The acute toxicity of catechol is relatively low. In humans, the irritant action of catechol can lead to dermatitis and other dermal lesions. Chronic oral treatment of rodents causes hyperplasia of the forestomach and pyloric mucosa.

Catechol was shown to cause gene mutations in mammalian cells *in vitro*. Chromosomal aberrations and sister chromatid exchanges were reported in mammalian cells in culture. After application to mice, catechol was negative in one and positive in three studies of micronucleus formation in bone marrow.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of catechol were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of catechol.

Overall evaluation

Catechol is *possibly carcinogenic to humans (Group 2B)*.

6. References

American Conference of Governmental Industrial Hygienists (1991*) Documentation of the Threshold Limit Values and Biological Exposure Indices*, 6th Ed., Vol. 1, Cincinnati, OH, pp. 239–240

American Conference of Governmental Industrial Hygienists (1997) *1997 TLVs® and BEIs®*, Cincinnati, OH, p. 18

Anderson, D., Yu, T.-W. & Schmezer, P. (1995) An investigation of the DNA-damaging ability of benzene and its metabolites in human lymphocytes, using the comet assay. *Environ. mol. Mutag.*, **26**, 305–314

Atchison, M., Chu, C.-S., Kakunaga, T. & Van Duuren, B.L. (1982) Chemical cocarcinogenesis with the use of a subclone derived from BALB/3T3 cells with catechol as cocarcinogen. *J. natl Cancer Inst.*, **69**, 503–508

Bhat, R.V., Subrahmanyam, V.V., Sadler, A. & Ross, D. (1988) Bioactivation of catechol in rat and human bone marrow cells. *Toxicol. appl. Pharmacol.*, **94**, 297–304

Bohrman, J.S., Burg, J.R., Elmore, E., Gulati, D.K., Barkfnecht, T.R., Niemeier, R.W., Dames, B.L., Toraason, M. & Langenbach, R. (1988) Interlaboratory studies with the Chinese hamster V79 cell metabolic cooperation assay to detect tumor-promoting agents. *Environ. mol. Mutag.*, **12**, 33–51

Budavari, S., ed. (1996) *The Merck Index*, 12th Ed., Whitehouse Station, NJ, Merck & Co., p. 1375

Chapman, D.E., Namkung, M.J. & Juchau, M.R. (1994) Benzene and benzene metabolites as embryotoxic agents: effects on cultured rat embryos. *Toxicol. appl. Pharmacol.*, **128**, 129–137

Chen, H. & Eastmond, D.A. (1995) Topoisomerase inhibition by phenolic metabolites: a potential mechanism for benzene's clastogenic effects. *Carcinogenesis*, **16**, 2301–2307

Ciranni, R., Barale, R., Ghelardini, G. & Loprieno, N. (1988a) Benzene and the genotoxicity of its metabolites. II. The effect of the route of administration on the micronuclei and bone marrow depression in mouse bone marrow cells. *Mutat. Res.*, **209**, 23–28

Ciranni, R., Barale, R., Marrazzini, A. & Loprieno, N. (1988b) Benzene and the genotoxicity of its metabolites. I. Transplacental activity in mice fetuses and in their dams. *Mutat. Res.*, **208**, 61–67

Erexson, G.L., Wilmer, J.L. & Kligerman, A.D. (1985) Sister chromatid exchange induction in human lymphocytes exposed to benzene and its metabolites *in vitro*. *Cancer Res.*, **45**, 2471–2477

Fahrig, R. (1984) Genetic mode of action of cocarcinogens and tumor promoters in yeast and mice. *Mol. gen. Genet.*, **194**, 7–14

Frantz, C.E., Chen, H. & Eastmond, D.A. (1996) Inhibition of human topoisomerase II *in vitro* by bioactive benzene metabolites. *Environ. Health Perspect.*, **104** (Suppl. 6), 1319–1323

Fukushima, S., Hagiwara, A., Hirose, M., Yamaguchi, S., Tiwawech, D. & Ito, N. (1991) Modifying effects of various chemicals on preneoplastic and neoplastic lesion development in a wide-spectrum organ carcinogenesis model using F344 rats. *Jpn. J. Cancer Res.*, **82**, 642–649

Furihata, C., Hatta, A. & Matsushima, T. (1989) Inductions of ornithine decarboxylase and replicative DNA synthesis but not DNA single strand scission or unscheduled DNA synthesis in the pyloric mucosa of rat stomach by catechol. *Jpn. J. Cancer Res*., **80**, 1052–1057

Garberg, P., Akerblom, E.L. & Bolcsfoldi, G. (1988) Evaluation of a genotoxicity test measuring DNA-strand breaks in mouse lymphoma cells by alkaline unwinding and hydroxyapatite elution. *Mutat. Res*., **203**, 155–176

Gopalakrishna, R., Chen, Z.H. & Gundimeda, U. (1994) Tobacco smoke tumor promoters, catechol and hydroquinone, induce oxidative regulation of protein kinase C and influence invasion and metastasis of lung carcinoma cells. *Proc. natl Acad. Sci. USA*, **91**, 12233–12237

Hagiwara, A., Tanak, H., Imaida, K., Tamano, S., Fukushima, S. & Ito, N. (1993) Correlation between medium-term multi-organ carcinogenesis bioassay data and long-term observation results in rats. *Jpn. J. Cancer Res.*, **84**, 237–245

Hamamoto, T. & Umemura, S. (1991) Phenol derivatives; catechol. In: Gerhartz, W. & Yamamoto, Y.S., eds, *Ullmann's Encyclopedia of Industrial Chemistry*, 5th rev. Ed., Vol. A1, New York, VCH Publishers, pp. 342–346

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W. & Zeiger, E. (1983) *Salmonella* mutagenicity test results for 250 chemicals. *Environ. Mutag*., **5** (Suppl. 1), 1–142

Hellmér, L. & Bolcsfoldi, G. (1992) An evaluation of the *E. coli* K-12 *uvrB/recA* DNA repair host-mediated assay. II. In vivo results for 36 compounds tested in the mouse. *Mutat. Res*., **272**, 161–173

Hirose, M., Inoue, T., Asamoto, M., Tagawa, Y. & Ito, N. (1986) Comparison of the effects of 13 phenolic compounds in induction of proliferative lesions of the forestomach and increase in the labelling indices of the glandular stomach and urinary bladder epithelium of Syrian golden hamsters. *Carcinogenesis*, **7**, 1285–1289

Hirose, M., Kurata, Y., Tsuda, H., Fukushima, S. & Ito, N. (1987) Catechol strongly enhances rat stomach carcinogenesis: a possible new environmental stomach carcinogen. *Jpn. J. Cancer Res.*, **78**, 1144–1149

Hirose, M., Fukushima, S., Shirai, T., Hasegawa, R., Kato, T., Tanaka, H., Asakawa, E. & Ito, N. (1990) Stomach carcinogenicity of caffeic acid, sesamol and catechol in rats and mice. *Jpn. J. Cancer Res.*, **81**, 207–212

Hirose, M., Wada, S., Yamaguchi, S., Masuda, A., Okazaki, S. & Ito, N. (1992) Reversibility of catechol-induced rat glandular stomach lesions. *Cancer Res.*, **52**, 787–790

Hirose, M., Fukushima, S., Tanaka, H., Asakawa, E., Takahashi, S. & Ito, N. (1993a) Carcinogenicity of catechol in F344 and B6C3F_1 mice. *Carcinogenesis*, **14**, 525–529

Hirose, M., Tanaka, H., Takahashi, S., Futakuchi, M., Fukushima, S. & Ito, N. (1993b) Effects of sodium nitrite and catechol, 3-methoxycatechol, or butylated hydroxyanisole in combination in a rat multiorgan carcinogenesis model. *Cancer Res.*, **53**, 32–37

IARC (1977) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 15, *Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals*, Lyon, pp. 155–173

IARC (1986) *IARC Monographs on the Carcinogenic Risks of Chemicals to Humans*, Vol. 38, *Tobacco Smoking*, Lyon

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Supplement 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, p. 59

International Labour Office (1991) *Occupational Exposure Limits for Airborne Toxic Substances*, 3rd Ed. (Occupational Safety and Health Series No. 37), Geneva, pp. 78–79

Irons, R.D., Stillman, W.S., Colagiovanni, D.B. & Henry, V.A. (1992) Synergistic action of the benzene metabolite hydroquinone on myelopoietic stimulating activity of granulocyte/macrophage colony-stimulating factor in vitro. *Proc. natl Acad. Sci. USA*, **89**, 3691–3695

Kawabe, M., Takaba, K., Yoshida, Y. & Hirose, M. (1994) Effects of combined treatment with phenolic compounds and sodium nitrite on two-stage carcinogenesis and cell proliferation in the rat stomach. *Jpn. J. Cancer Res.*, **85**, 17–25

Kolachana, P., Subrahmanyam, V.V., Meyer, K.B., Zhang, L. & Smith, M.T. (1993) Benzene and its phenolic metabolites produce oxidative damage in HL60 cells *in vitro* and in the bone marrow *in vivo*. *Cancer Res.*, **53**, 1023–1026

Krumenacker, L., Costantini, M., Pontal, P. & Sentenac, J. (1995) Hydroquinone, resorcinol, and catechol. In: Kroschwitz, J.I. & Howe-Grant, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th Ed., Vol. 13, New York, John Wiley, pp. 996–1014

Kurata, Y., Fukushima, S., Hasegawa, R., Hirose, M., Shibata, M.-A., Shirai, T. & Ito, N. (1990) Structure-activity relations in promotion of rat urinary bladder carcinogenesis by phenolic antioxidants. *Jpn. J. Cancer Res.*, **81**, 754–759

La Voie, E.J., Shigematsu, A., Mu, B., Rivenson, A. & Hoffmann, D. (1985) The effects of catechol on the urinary bladder of rats treated with *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine. *Jpn. J. Cancer Res. (Gann)*, **76**, 266–171

Leanderson, P. & Tagesson, C. (1990) Cigarette smoke-induced DNA-damage: role of hydroquinone and catechol in the formation of the oxidative DNA-adduct, 8-hydroxydeoxyguanosine. *Chem.-biol. Interact.*, **75**, 71–81

Lévay, G. & Bodell, W.J. (1996) Role of hydrogen peroxide in the formation of DNA adducts in HL-60 cells treated with benzene metabolites. *Biochem. biophys. Res. Comm.*, **222**, 44–49

Lewis, R.J., Jr (1993) *Hawley's Condensed Chemical Dictionary*, 12th Ed., New York, Van Nostrand Reinhold, p. 981

Lewis, J.G., Stewart, W. & Adams, D.O. (1988) Role of oxygen radicals in induction of DNA damage by metabolites of benzene. *Cancer Res.*, **48**, 4762–4765

Li, Q., Aubrey, M.T., Christian, T. & Freed, B.M. (1997) Differential inhibition of DNA synthesis in human T cells by the cigarette tar components hydroquinone and catechol. *Fundam. appl. Toxicol.*, **38**, 158–165

Lide, D.R., ed. (1997) *CRC Handbook of Chemistry and Physics*, 78th Ed., Boca Raton, FL, CRC Press, p. 3-43

Manning, B.W., Adams, D.O. & Lewis, J.G. (1994) Effects of benzene metabolites on receptor-mediated phagocytosis and cytoskeletal integrity in mouse peritoneal macrophages. *Toxicol. appl. Pharmacol.*, **126**, 214-223

Marrazzini, A., Chelotti, L., Barrai, I., Loprieno, N. & Barfale, R. (1994) In vivo genotoxic interactions among three phenolic benzene metabolites. *Mutat. Res.*, **341**, 29–46

Maruyama, H., Amanuma, T., Nakae, D., Tsutsumi, M., Kondo, S., Tsujiuchi, T., Denda, A. & Konishi, Y. (1991) Effects of catechol and its analogs on pancreatic carcinogenesis initiated by *N*-nitrosobis(2-oxopropyl)amine in Syrian hamsters. *Carcinogenesis*, **12**, 1331–1334

Maruyama, H., Amanuma, T., Tsutsumi, M., Tsujiuchi, T., Horiguchi, K., Denda, A. & Konishi, Y. (1994) Inhibition by catechol and di(2-ethylhexyl)phthalate of pancreatic carcinogenesis after initiation with *N*-nitrosobis(2-hydroxypropyl)amine in Syrian hamsters. *Carcinogenesis*, **15**, 1193–1196

McGregor, D.B., Riach, C.G., Brown, A.., Edwards, I., Reynolds, D., West, K. & Willington, S. (1988) Reactivity of catecholamines and related substances in the mouse lymphoma L5178Y cell assay for mutagens. *Environ. mol. Mutag*., **11**, 523–544

Melikian, A.A., Jordan, K.G., Braley, J., Rigotty, J., Meschter, C.L., Hecht, S.S. & Hoffmann, D. (1989) Effects of catechol on the induction of tumors in mouse skin by 7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrenes. *Carcinogenesis*, **10**, 1897–1900

Mirvish, S.S., Salmasi, S., Lawson, T.A., Pour, P. & Sutherland, D. (1985) Test of catechol, tannic acid, *Bidens pilosa*, croton oil, and phorbol for cocarcinogenesis of esophageal tumors induced in rats by methyl-*n*-amylnitrosamine. *J. natl Cancer Inst.*, **74**, 12831290

Miyata, Y., Fukushima, S., Hirose, M., Masui, T. & Ito, N. (1985) Short-term screening of promoters of bladder carcinogenesis in *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine-initiated unilaterally ureter-ligated rats. *Jpn. J. Cancer Res. (Gann)*, **76**, 828–834

Moran, J.L., Siegel, D., Sun, X.-M. & Ross, D. (1996) Induction of apoptosis by benzene metabolites in HL60 and CD34 human bone marrow progenitor cells. *Mol. Pharmacol.*, **50**, 610-615

Morimoto, K. (1983) Induction of sister chromatid exchanges and cell division delays in human lymphocytes by microsomal activation of benzene. *Cancer Res.*, **43**, 1330–1334

Morimoto, K. & Wolff, S. (1980) Cell cycle kinetics in human lymphocyte cultures. *Nature*, **288**, 604–606

Nakamura, S.-I., Oda, Y., Shimada, T., Oki, I. & Sugimoto, K. (1987) SOS-inducing activity of chemical carcinogens and mutagens in *Salmonella typhimurium* TA1535/pSK1002: examination with 151 chemicals. *Mutat. Res*., **192**, 239–246

Nazar, M.A., Rapson, W.H., Brook, M.A., May, S. & Tarhanen, J. (1981) Mutagenic reaction products of aqueous chlorination of catechol. *Mutat. Res*., **89**, 45–55

Neun, D.J., Penn, A. & Snyder, C.A. (1992) Evidence for strain-specific differences in benzene toxicity as a function of host target cell susceptibility. *Arch. Toxicol.*, **66**, 11–17

NOES (1997) *National Occupational Exposure Survey 1981–83*, Unpublished data as of November 1997, Cincinnati, OH, United States Department of Health and Human Services, Public Health Service, National Institute for Occupational Safety and Health

Ohgaki, H., Szentirmay, Z., Take, M. & Sugimura, T. (1989) Effect of 4-week treatment with gastric carcinogens and enhancing agents on proliferation of gastric mucosa cells in rats. *Cancer Lett.*, **46**, 117–122

Okazaki, S., Hoshiya, T., Takahashi, S., Futakuchi, M., Saito, K. & Hirose, M. (1993) Modification of hepato- and renal carcinogenesis by catechol and its isomers in rats pretreated with *N*-ethyl-*N*-hydroxyethylnitrosamine. *Teratog. Carcinog. Mutag*., **13**, 127–137

Pellack-Walker, P. & Blumer, J.L. (1986) DNA damage in L5178YS cells following exposure to benzene metabolites. *Mol. Pharmacol.*, **30**, 42–47

Robertson, M.L., Eastmond, D.A. & Smith, M.T. (1991) Two benzene metabolites, catechol and hydroquinone, produce a synergistic induction of micronuclei and toxicity in cultured human lymphocytes. *Mutat. Res.*, **249**, 201–209

Schaeffer, D., Jürgensmeier, J.M. & Bauer, G. (1995) Catechol interferes with TGF-β-induced elimination of transformed cells by normal cells: implications for the survival of transformed cells during carcinogenesis. *Int. J. Cancer*, **60**, 520–526

Seidel, H.J., Barthel, E., Schäfer, F., Schad, H. & Weber, L. (1991) Action of benzene metabolites on murine hematopoietic colony-forming cells *in vitro*. *Toxicol. appl. Pharmacol.*, **111**, 128–131

Shibata, M.A., Hirose, M., Yamada, M., Tatematsu, M., Uwagawa, S. & Ito, N. (1990a) Epithelial cell proliferation in rat forestomach and glandular stomach mucosa induced by catechol and analogous dihydroxybenzenes. *Carcinogenesis*, **11**, 997–1000

Shibata, M.A., Yamada, M., Hirose, M., Asakawa, E., Tatematsu, M. & Ito, N. (1990b) Early proliferative responses of forestomach and glandular stomach of rats treated with five different phenolic antioxidants. *Carcinogenesis*, **11**, 425–429

Smith, M.T., Yager, J.W., Steinmetz, K.L. & Eastmond, D.A. (1989) Peroxidase-dependent metabolism of benzene's phenolic metabolites and its potential role in benzene toxicity and carcinogenicity. *Environ. Health Perspect.*, **82**, 23–29

Snyder, R., Dimitriadis, E., Guy, R., Hu, P., Cooper, K., Bauer, H., Witz, G. & Goldstein, B.D. (1989) Studies on the mechanism of benzene toxicity. *Environ. Health Perspect.*, **82**, 31–35

Solveig Walles, S.A. (1992) Mechanisms of DNA damage induced in rat hepatocytes by quinones. *Cancer Lett.*, **63**, 47–52

Stenius, U., Warholm, M., Rannug, A., Walles, S., Lundberg, I. & Högberg, J. (1989) The role of glutathione depletion and toxicity in hydroquinone-induced development of enzyme-altered foci. *Carcinogenesis*, **10**, 593–599

Subrahmanyam, V.V., Kolachana, P. & Smith, M.T. (1990) Effect of phenol and catechol on the kinetics of human myeloperoxidase-dependent hydroquinone metabolism. *Adv. exp. Med. Biol.*, **283**, 377–381

Tanaka, H., Hirose, M., Hagiwara, A., Imaida, K., Shirai, T. & Ito, N. (1995) Rat strain differences in catechol carcinogenicity to the stomach. *Food chem. Toxicol.*, **33**, 93–98

Tatematsu, M., Ichinose, M., Tsukada, S., Kakei, N., Takahashi, S., Ogawa, K., Hirose, M., Furihata, C., Miki, K., Kurokawa, K. & Ito, N. (1993) DNA methylation of the pepsinogen 1 gene during rat glandular stomach carcinogenesis induced by *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine or catechol. *Carcinogenesis*, **14**, 1415–1419

Tsutsui, T., Hayashi, N., Maizumi, H., Huff, J. & Barrett, J.C. (1997) Benzene-, catechol-, hydroquinone- and phenol-induced cell transformation, gene mutations, chromosome aberrations, aneuploidy, sister chromatid exchanges and unscheduled DNA synthesis in Syrian hamster embryo cells. *Mutat. Res.*, **373**, 113–123

Tunek, A., Hogstedt, B. & Olofsson, T. (1982) Mechanism of benzene toxicity. Effects of benzene and benzene metabolites on bone-marow cellularity of granulopoietic stem cells and frequency of micronuclei in mice. *Chem.-biol. Interact.*, **39**, 129–138

United States National Library of Medicine (1997*) Hazardous Substances Data Bank (HSDB)*, Bethesda, MD [Record No. 1436]

Van Duuren, B.L., Melchionne, S. & Seidmann, I. (1986) Phorbol myristate acetate and catechol as skin cocarcinogens in Sencar mice. *Environ. Health Perspect.*, **68**, 33–38

Verschueren, K. (1996) *Handbook of Environmental Data on Organic Chemicals*, 3rd Ed., New York, Van Nostrand Reinhold, pp. 429–431

Wangenheim, J. & Bolcsfoldi, G. (1988) Mouse lymphoma L5178Y thymidine kinase locus assay of 50 compounds. *Mutagenesis*, **3**, 193–205

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

Yager, J.W., Eastmond, D.A., Robertson, M.L., Paradisin, W.M. & Smith, M.T. (1990) Characterization of micronuclei induced in human lymphocytes by benzene metabolites. *Cancer Res*., **50**, 393–399

Yamaguchi, S., Hirose, M., Fukushima, S., Hasegawa, R. & Ito, N. (1989) Modification by catechol and resorcinol of upper digestive tract carcinogenesis in rats treated with methyl-*n*-amylnitrosamine. *Cancer Res.*, **49**, 6015–6018

Yoshida, D. & Fukuhara, Y. (1983) Mutagenicity and co-mutagenicity of catechol on *Salmonella*. *Mutat. Res*., **120**, 7–11