p-tert-Butylcatechol
98-29-3

NTP NOMINATION HISTORY AND REVIEW

A. Nomination History

1. Nomination Source: National Cancer Institute

2. Recommendations: Carcinogenicity

3. Rationale/Remarks:
   - Industrial chemical with high and increasing level of production and usage
   - Potential for human exposure
   - Suspicion of carcinogenicity
   - FDA's interest in potential toxicity of antioxidants
   - Interest in evaluating the toxicity of the dihydroxybenzenes chemical class of antioxidants

4. Priority: High

5. Date of Nomination: 4/93

B. Interagency Committee for Chemical Evaluation and Coordination Review

1. Date of Review:

2. Recommendations:

3. Priority:

4. NTP Chemical Selection Principles:

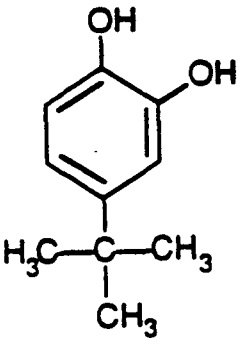
5. Rationale/Remarks:

SUMMARY OF DATA FOR CHEMICAL SELECTION

CHEMICAL IDENTIFICATION

CAS Registry Name:	98-29-3
Name:	4-*tert*-Butylcatechol
Synonyms and Trade Names:	1,2-Benzenediol, 4-(1,1-dimethylethyl)-(9CI); Pyrocatechol, 4-*tert*-butyl-(8CI); 4-*tert*-Butyl-1,2-benzenediol; 4-*tert*-Butyl-1,2-dihydroxybenzene; 1,2-Dihydroxy-4-*tert*-butylbenzene; TBC; PTBC; 4-TBC.

Structure, Molecular Formula and Molecular Weight



$C_{10}H_{14}O_2$ Mol. wt.: 166.2

Chemical and Physical Properties

Description:	Colorless to white crystalline or waxy solid (Verschueren, 1983)
Boiling Point:	285°C (Sax & Lewis, 1987)
Melting Point:	56-58°C (≥99% purity); 53-56°C (≥98% purity) (Fluka, 1990; Verschueren, 1983)
Solubility:	Soluble in ether, alcohol, acetone, trifluloroacetic acid; slightly soluble in water (0.2 wt% @25°C) (Sax & Lewis, 1987; Verschueren, 1983)

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Density:	1.049 (60°/25°C) (Sax & Lewis, 1987; Verschueren, 1983)
Vapor Pressure:	0.0028 mm @25°C (Verschueren, 1983)
Flash Point:	265°F (129°C) (Sax & Lewis, 1987)
Stability:	Combustible when exposed to heat or flame; emits acrid and irritating fumes when heated to decomposition (Sax & Lewis, 1989)

Technical Products and Impurities: 4-*tert*-Butylcatechol is manufactured by reacting isobutylene with catechol in the presence of ion exchange resins (Varagnat, 1980). 4-*tert*-Butylcatechol is available in HPLC grade (>99%), technical grade (≥98% purity), and practical grade. Depending on storage and/or shipping conditions, this material can be a viscous yellow to orange liquid or white to tan crystalline solid. Typically, this material is sold as a powder or in 85% methanol or water solution. The only reported impurity is 0.5% 3,5-di-*tert* butylpyrocatechol, measured by GC analysis (Riedel-de Haen, 1984).

BASIS OF NOMINATION TO THE CSWG

p-*tert*-Butylcatechol is an industrial chemical which has a moderate and growing level of production and usage. This compound was brought to the CSWG because of reports in the recent chemical marketing press that increasing production and consumption are likely in the nineties. There is a twenty year history of documented industrial exposures to this substance resulting in chemical leukoderma. In addition, TBC-containing products such as shoes, artificial limbs and rubber gloves have elicited allergic responses attributed to the presence of TBC in exposed members of the general population.

Recent studies have called attention to the tumor promoting ability of butylcatechol and resulted in the postulation of a possible role in human gastric carcinogenesis. Interest has been shown in evaluating various members of the dihydroxybenzene class of commercial antioxidant and related compounds; but, to date, neither t-butylcatechol, nor its parent, catechol, have been tested in a full 2 year carcinogenicity bioassay.

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SELECTION STATUS

ACTION BY CSWG: 6/07/91

Studies Requested: Carcinogenicity bioassay

Priority: High

Comments: Recommendation made that it be presented to the NTP at the same time catechol is presented. Although p-t-butylcatechol has been used for a long period of time, neither it nor its parent, catechol, has been tested in a full 2-year carcinogenicity bioassay. p-t-Butylcatechol is expected to follow metabolic pathways similar to its parent, catechol, which is absorbed both from the GI tract and through the skin and is excreted in the urine, principally as the ethereal sulfate. The FDA has shown some concern about antioxidants. It was opined that the dosage range used in testing is going to be very important because so many of the antioxidants have beneficial effects up to a certain concentration.

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EXPOSURE INFORMATION

Commercial Availability:

Production and Producers: United States demand for 4-*tert*-butyl catechol has been estimated as 1.5 million lbs/yr for 1989. However, total consumption and new domestic production are expected to be substantially increased over the next few years (Chemical Marketing Reporter, January 23, 1989). Eight producers have been cited in 1990's *Directory of World Chemicgl Producers*. They are: Crown Zellerbach Corporation, Specialty Chemicals (USA), R-M Industries, Inc. (USA), Dainippon Ink & Chemicals Inc. (Japan), Ube Industries, Ltd. (Japan), Societe Francaise d'Organo-Synthese S.A. (France), Coalite Fuels & Chemicals, Ltd. (Great Britain), Ward Blenkinsop & Co., Ltd. (Great Britain), and Brichima-Enichem Sintesi, S.p.A. (Italy). EPA's TSCA plant and production database (TSCAPP) was searched for companies reporting manufacture or importation of t-butylcatechol. Table 1 summarizes the data contained therein; however, this database was made available through the Chemical Information System (CIS) in 1983, and the information it contains may not be up-to-date and serves mainly as an indicator of TBC usage in the United States in the 1980s.

Table 1. Reporting companies and annual production/import volumes for TBC (TSCAPP)

	Manufacturer	Importer	Volume Range, lbs.
Aceto Chemical Co.		x	N*
Crown Zellerbach	x		N*
Dainippon Ink & Chemicals (DIC)		x	100,000-1,000,000
Dow Chemical Co.	x		N*
Gallard-Schlesinger		x	N*
Millmaster Chemical Co.	x		10,000-100,000
Petro-Tex Chemical Corp. (TX)		x	1,000-10,000
Petro-Tex Chemical Corp. (NJ)		x	1,000-10,000

*N = volume not reported

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In the mid- to late-eighties R-M Industries Inc. had the largest TBC manufacturing plant in the U.S. Since 1989, R-M manufactured TBC exclusively for Rhone-Poulenc, presently the largest catechol supplier to the U.S. market. R-M Industries announced that they will stop production of *tert*-butylcatechol at the end of 1990, and the manufacturing of this compound will be assumed by Rhone-Poulenc. Rhone-Poulenc completed a buyout of U.S. Producers, Neville-Synthese Organics and R-M Industries, Inc., in 1989, and started to build a $100-150 million plant at Baton Rouge, LA. It is unclear how quickly and to what extent Rhone-Poulenc will manufacture TBC in the U.S. (rather than import from Europe) once R-M has stopped its production of TBC and R-P's Baton Rouge plant has started to produce catechol domestically. Dow Chemical, Inc., a former producer, stopped its production a few years ago due to the lack of sufficient profit margin.

Imports: DIC Americas/Metrichem is the largest importer of TBC in the U.S. This company sells material made in Japan by Dainippon Ink & Chemicals Co. Whereas R-M Industries obtained its catechol supplies from Rhone-Poulenc, DIC produces its TBC from catechol raw material supplied by UBE Industries (Japan). The only available information indicate that DIC Americas/Metrichem imported 100,000 to 1,000,000 pounds of TBC in 1983 (CIS/TSCAPP database). Neville-Synthese Organics and R-M Industries sold their marketing rights to Rhone-Poulenc who will import this compound as well as build up domestic production of TBC. It is expected that the current import quantity is significantly higher than the 1983 level. In Brazil, the Conselho de Desenvolvimento Industrial (CDI) obtained government approval on a project to build a multi-purpose plant to manufacture chemicals including TBC (1987). When this unit comes on stream, it will increase by another 150 ton/yr, the capacity for TBC in the world market. Other importers/suppliers include: Gallard-Schlesinger, Maypro, Penta, SST, Schweizerhall, Spectrum, Wall and others.

Use Pattern: 4-*tert*-Butylcatechol is principally used as an antioxidant, stabilizer, and polymerization inhibitor for styrene, butadiene, neoprene, and other olefins and reactive monomers. Other reported uses include antiskinning additive; corrosion inhibitor; activator for insecticides; clay strengthener in building materials; and radical inhibitor, according to the STN, 1991. Deichmann *et al.* (1981) list the following additional uses for TBC in *Patty's*

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Industrial Hygiene and Toxicology: phenolic-type germicide, emulsion breaker, pour point depressant, chemical intermediate for organic syntheses, and as a component of resins used as shoe adhesives.

When used as an antioxidant in styrene monomer, the typical additive level of TBC to the styrene monomer is 10-50 ppm with a half-life of 6-10 weeks under ambient conditions. TBC is also a common inhibitor/stabilizer for isoprene and chloroprene, added at a recommended level of 50 ppm to prevent bulk polymerization particularly when storage will be prolonged or at a temperature ≥0°C (Johnson, P.R., 1979; Saltman, W.M., 1981). It is also reported to be used as a polymerization inhibitor in photopolymer plate-making systems for printing plate manufacture (Malten, 1982).

The Occupational Safety and Health Administration (OSHA) has developed a monitoring procedure to sample and analyze low ppm concentrations of 1,3-butadiene in ambient air which uses TBC, coated at 10% by weight, on coconut shell charcoal (Hendricks & Schultz, 1986). This compound has also been proposed for investigation as a potential therapeutic agent in the treatment of Alzheimer's disease (Furukawa *et al.*, 1990).

Other recent developments, proposed uses and high tech applications for TBC were found in a search of the Chemical Abstracts database (STN, 1991), including:

- component of liquid photopolymerizable (UV) protective cover coatings in fabrication of electric circuits, photoresists and solder masks (Bell Telephone Laboratories, Inc.; Asahi Chemical Co., Ltd.)

- component at 5-40 wt% of a photoresist remover (Tokyo Ohka Kogyo Co., Ltd.)

- component of photographic stabilizer for latent image stabilization; photographic development accelerator for direct-positive photographic film (Konishiroku Photo Industry Co., Ltd.)

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- anticorrosion agent in magnetic recording materials (Matsushita Electric Industrial Co., Ltd.)

Human Exposure: Occupational exposure to phenolic and catecholic compounds has been found to be a common factor in the development of leukoderma with depigmentation (Gellin *et al.*, 1979). Exposures to p-*tert*-butylcatechol by skin contact have been documented in Chemical Process Industry (CPI) workers involved in both the production and further processing of TBC. Exposures to workers engaged in the production of this compound were studied, and a direct correlation was observed between gas-liquid chromatography (GLC) measurements of urinary concentrations of TBC and levels of exposure in the work place (Ikeda *et al.*, 1978). Exposures to factory workers were reported to be higher for product packers than plant operators or engineers, as determined by GLC urinalysis. The National Occupational Exposure Survey (NOES), 1983, has released the following data about exposures: 1692 facilities involved in 23 industries; 27,464 workers (of which 4,292 were female) representing 40 occupations (NLM/RTECS database).

The following instances of occupational and/or consumer exposures to TBC have been reported in various literature sources.

- Occupational allergic dermatitis with depigmentation (leukoderma) was reported in polyvinylchloride chemical plant workers after documented exposures to TBC. One sensitized worker subsequently developed local lesions from contact with PVC in shoes which the author determined were caused by free TBC in the PVC-containing footwear products. TBC has been found to leach from adhesive resins used in shoemaking (Laure, 1984).

- Leukoderma developed on the hands, arms and face of a polyester resin plant worker who handled TBC powder. The depigmentation which accompanied the allergic dermatitis was reduced in size but still present 3 years after the exposures took place (Horio *et al.*, 1977).

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- TBC from rubber gloves worn by a hotel worker determined to be the cause of this black woman's chemically-induced dermatitis with depigmentation (Gellin, 1983).

- Contact with rubber gloves was also investigated as a possible source of TBC-induced leukoderma of hands and forearms; worker exposures to TBC-containing assembly oils were considered a possible cause as well (Gellin *et al.*, 1970).

- Out of a group of 75 workers in a Michigan tappet assembly plant considered at risk for handling a TBC-containing assembly lubricating oil, 4 developed occupational leukoderma (Gellin *et al.*, 1970).

- In a survey of office workers, such as secretaries, architects' clerks, photographers, and photoprocessing assistants who used duplicating processes, TBC was identified as the chemical most frequently causing sensitization from contact with Thermofax duplicating papers (Foussereau *et al.*, 1982).

- Newspaper production workers have developed allergic contact dermatitis from TBC used as an antioxidant in GAF type S phototypesetting paper (Fardal & Curphey, 1983).

- Consumer exposures to TBC include users of medical prostheses. p-*tert*-Butylcatechol has been identified as a contact allergen leaching from both polyester- and polyacrylic-based artificial limbs (Macfarlane *et al.*, 1990).

- t-Butylcatechol-containing styrene is widely used and exposures to the TBC-stabilized monomer used in the manufacture of fiberglass-reinforced polyester products, such as boats, have been reported to occur over a wide range of concentrations.

- Although there is no evidence that TBC is currently used in cosmetics, Gagliardi *et al.* (1989) have proposed an HPLC method for determining TBC levels in cosmetic products for monitoring purposes.

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- Finally, leukomelanodermatoses have been attributed to melanogenesis-interrupting phenolic germicides and synthetic detergents, possibly containing TBC (Hirosawa *et al.*, 1982; McGuire & Hendee, 1971).

Environmental Occurrence: Catechol derivatives are found at appreciable levels in the environment; and t-butylcatechol, specifically, can be considered a chemical substance of environmental significance, according to Hirose *et al.* (1989). Gagliardi *et al.* (1989), who reported developing an analytical method for the determination of TBC in vanishing creams (for compliance with an EEC directive), cited other analytical methods for the determination of this compound, described as one of the numerous dihydroxybenzene compounds and derivatives found in the environment.

TBC is a known impurity (as residual additive) of 1,3-butadiene which is used extensively in synthetic rubber manufacturing. Pullinger *et al.* (1979) identified this compound in the atmosphere of the exposure chamber during inhalation toxicity studies being carried out on butadiene.

Regulatory Status: No occupational standards for exposure to p-*tert*-butylcatechol have been established by OSHA. Though the ACGIH has not issued a Threshold Limit Value (TLV) recommendation for TBC, this group recommends an 8-hour time weighted average TLV of 5 ppm (20 mg/m^3) for parent compound, catechol (Anon, 1990).

The European Communities Commission has acted to exclude the use of TBC as a depigmenter in commercial cosmetic creams in Departmental Order 24.11.87 n. 53 (Annex II) of Directive 87/137 EEC (Gagliardi *et al.*, 1989).

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports specifically associating t-butyl catechol exposure with cancer risk in humans were found in the published literature. However, Thomas and Waxweiler (1986), in a review of occupational risk factors in elevated incidence of brain tumors, determined that phenols and phenolic compounds were one of six categories of agents common to certain occupational groups with elevated brain tumor risk. Of the 26 occupational groups evaluated, 14 were potentially exposed to phenols and phenolic compounds, along with one or more of the other five categories of compounds (see Table 2).

Santodonato *et al.* (1985) found an absence of epidemiological studies addressing cancer risk associated with TBC-stabilized styrene monomer usage in the fiberglass-reinforced polyester products industry. However, an elevated occurrence of hematopoietic and lymphatic system neoplasms has been found in the styrene-butadiene rubber industry where TBC is used as polymerization inhibitor.

TBC is a skin and eye irritant and is moderately toxic by ingestion and dermal absorption. Phenol-like systemic toxic effects might be expected to occur, as with the parent compound catechol (Deichmann & Keplinger, 1981). Numerous cases of allergic dermatitis, leukoderma and vitiligo, a chronic and progressive anomaly of skin pigmentation, have been reported during the past twenty years. In cases of occupational leukoderma, histologic examinations have revealed a decrease in melanin and the number of dopa-positive melanocytes in the basal layer of the skin at the lesion site.

Picardo *et al.* (1987) compared TBC and other diphenolic derivatives which act as tyrosinase substrates with analogs which do not function as substrates for tyrosinase enzymes to determine substrate stability and oxidative mechanisms relative to their toxicity on different cell lines. This study was conducted *in vitro* using Raje and K 562 cell lines which lack tyrosinase, and 1RE 1 and 1RE 2 human melanoma cell lines. The authors found that catechols (including TBC) which are substrates of tyrosinase were equally toxic to melanoma

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Table 2. Common occupational exposure among groups with elevated brain tumor risk (from Thomas & Waxweiler, 1986)

Occupational group potentially exposed	Exposure					
	Organic solvents	Lubricating oils	Acrylonitrile or vinyl chloride	Formalydehyde	Polycyclic aromatic hydro carbons	Phenols and phenolic compounds
Acrylonitrile polymerization workers	x	.	x	.	.	.
Airplane mechanics and repairmen	x	x	.	.	x	.
Aluminum reduction plant workers	x	.	.	.	x	.
Anatomists	.	.	.	x	.	x
Artists	x	.	.	.	.	.
Bus mechanics	x	x	.	.	x	.
Chemists	x	.	.	.	.	x
Cosmetologists	.	.	.	x	.	x
Electricians	x	.	.	.	.	.
Embalmers	.	.	.	x	.	x
Farmers and agricultural workers	x	x	.	.	.	x
Formaldehyde production workers	.	.	.	x	.	.
Machinists	x	x	.	.	x	.
Motor vehicle examiners	.	.	.	.	x	.
Nuclear fuels & weapons fabrication	x	x	.	.	x	.
Nurses	.	.	.	.	.	x
Oil refinery workers	x	x	.	.	x	x
Pathologists	.	.	.	x	.	x
Pattern makers - metal	x	x	.	.	.	.
Petrochemical plant workers	x	.	.	.	.	x
Pharmaceutical workers	x	.	.	x	.	x
Photographic process workers	x	.	.	x	.	x
Polyvinyl chloride production workers	x	.	x	.	.	.
Rubber workers	x	.	x	.	x	x
Textile workers	x	.	.	x	.	x
Veterinarians	.	.	.	x	.	x

and non-melanoma cell lines. In chemically-induced leukoderma, a selective melanacytotoxic action on functional melanocytes was observed, and the authors proposed that a competitive inhibition of the enzyme, tyrosinase, may be involved (Gellin & Maibach,

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1983). Usami *et al.* (1980) suggested that tyrosinase activity is inhibited by TBC at the second step of melanogenesis. Yonemoto *et al.* (1983a & b) studied the effects of TBC on enzyme activity, eumelanin content and amount of sulfur in cultured human melanoma cells and concluded that this chemical alters the types of melanin formed by modulation of glutathione reductase and γ-glutamyl transpeptidase activity. Elucidation of the mechanism of depigmentation was undertaken in a tissue cultured B16 melanoma cell line study. Elevation of glutathione-metabolizing enzyme activity at a 10^{-4}M concentration of TBC was considered evidence that TBC stimulates pheomelanogenesis in melanocytes (Kawashima *et al.*, 1984).

Carcinogenicity: Hirose *et al.* (1989) have speculated that p-*tert*-butylcatechol and other catechol derivatives may be weak, nongenotoxic stomach carcinogens with promoting activity. Their conclusions are based on evidence from promotion studies of 1 year's duration in rats.

Animal Data: In tumor promotion studies TBC, when administered in the diet, significantly enhanced forestomach and glandular stomach carcinogenicity in rats pretreated with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). TBC alone induced significant hyperplasia in the forestomach but not in the glandular stomach in 52 week studies by Hirose *et al.* (1989) designed to determine the modifying effects of TBC and other dihydroxybenzene compounds on the development of stomach epithelium tumors in rats after initiation with MNNG. In these studies a group of 16 six week old F344 rats received a single intragastric dose of MNNG at 150 mg/kg of body weight in dimethyl sulfoxide. Starting one week later, the animals received a powdered diet containing 1.5% TBC *ad libitum* until week 52. Over the same period, 15 rats were given 1.5% TBC-supplemented diet alone without MNNG pretreatment. Hyperplasia was seen in the forestomachs of all 16 rats in the MNNG treated group as well as the following incidences of forestomach tumors: papillomas, 15(93.8%); carcinomas *in situ*, 4(25%) and squamous cell carcinomas, 12(75%). Moderate or severe forestomach hyperplasia was also found in all 15 of the rats treated with TBC alone, with 4(26.7%) of them showing a severe level of hyperplasia. In addition, one animal (6.7%) in this TBC-only group was reported to have developed a papilloma.

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In another study (Hirose *et al.*, 1988), the incidence of adenomatous hyperplasia in the rat glandular stomach (pyloric region) was reported as significantly higher ($P<0.05$) in animals pretreated with MNNG followed by TBC than in control group animals. Adenomatous hyperplasia was found in 5(31.3%) of the animals while 3 animals (18.8%) developed adenocarcinoma. No lesions were observed in the fundic region of the glandular stomach. TBC alone did not induce any lesions in either the fundic or pyloric region of the glandular stomach, and there were no incidences in the control group.

Several research groups have conducted experiments to elucidate cellular-level depigmentation effects of t-butylcatechol. Yonemoto *et al.* (1983a) studied the effect of TBC (1M in DMSO 3V:7V) in 3 successive 0.3 ml topical applications 48 hours apart to the ear skin of hairless mice (Uscd strain) on glutathione reductase (GR) activity. They observed elevated GR activity with pheomelanogenesis resulting from altered melanosomes which preceded melanocyte degeneration and pigment loss in skin.

The following acute toxicity information for t-butylcatechol is available in the published literature (Sax and Lewis, 1989; Smyth *et al.*, 1954).

Rat oral LD_{50}: 2820 mg/kg
Mouse intravenous LD_{50}: 32 mg/kg
Rabbit dermal LD_{50}: 630 mg/kg

Irritation data in the same source include the following:

Rabbit dermal, 500 mg/24 hr - severe
Rabbit eye, 50 g open - severe
Guinea pig dermal, 1%/3 wk - moderate
Guinea pig dermal, 0.1%/3 wk - mild

Mansur *et al.*, 1978, investigated the effect of TBC on tissue cultured melanocytes from adult guinea pig epidermis. On the 5th day of culture, Petri dishes with large numbers of

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melanocytes were treated with enough TBC dissolved in DMSO to achieve final TBC concentrations of 0.5 x 10^{-3} to 3 x 10^{-3} mg/ml of culture medium. After 6 hours the mid-range concentration of 1.5 x 10^{-3} mg/ml was cytotoxic to about 30% of the melanocytes and about half of the remaining melanocytes showed reversible changes in cell shape. Increased numbers of cell deaths were seen when the TBC concentration was increased. The authors postulated that TBC-induced depigmentation *in vivo* was the result of melanocyte damage and death probably caused by free radical lipid peroxidation.

Short-Term Tests: p-*tert*-Butylcatechol was mutagenic in the mouse lymphoma L5178Y cell mutation assay at concentrations ranging from 4.0 to 5.0 g/ml (McGregor *et al.*, 1988).

Dean *et al.* (1985) tested TBC and 40 other industrial chemicals in the Ames bacterial mutation assay, in *Saccharomyces cerevisiae* JD1 for mitotic gene conversion, and in a cultured rat liver cell line for structural chromosome damage. TBC (>95% purity) in a DMSO formulation was negative for genotoxicity in all of the test systems, which included the following: *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 both with and without S-9 activation; *E. coli* WP_2 and WP_2 uvrA both with and without S-9; S. cerevisiae JD1 both with and without S-9; rat liver chromosome assay.

Vainio *et al.* (1976), in a study of the mutagenic activity of styrene and styrene oxide in the Ames *Salmonella* system, also tested TBC present as a preservative agent/stabilizer in the monomer. They reported that t-butylcatechol was non-mutagenic in 5 strains (TA98, TA100, TA1535, TA1537 and TA1538) both with and without S-9 liver microsomal enzyme activation.

Metabolism: t-Butylcatechol is expected to follow metabolic pathways similar to its parent, catechol, which is absorbed both from the GI tract and through the skin and is excreted in the urine, principally as the ethereal sulfate. The liver is the likely site of formation of oxidative metabolites of TBC mainly via sulfhydryl and glutathione conjugation followed by urinary excretion. Other minor metabolic pathways described for analogs, such as metabolic oxidation to the corresponding trihydroxybenzene derivative or alkylation of one

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of the phenolic hydroxy groups may occur (Sandmeyer, 1981). Hirose *et al.* (1989) cited several *in vitro* studies which provided some details pertinent to the metabolism of TBC though not the underlying mechanisms. Derivatives of catechol were found to undergo perioxidative oxidation which proceeds through oxidation-reduction cycling to produce the corresponding quinone metabolites or active oxygen species that interact with cellular macromolecules.

Marchesini *et al.* (1977) reported that 4-TBC yielded the corresponding o-quinone via a secondary catecholoxidase activity of the enzyme, ascorbate oxidase, found in fruits and vegetables.

In an *in vitro* study, Picardo *et al.* (1987) report that TBC decomposed within 24 hours. In a study of microbial degradation of commercial styrene in soil and enrichment cultures, Sielicki *et al.* (1978) found that TBC, present as an antioxidant/polymerization inhibitor, was microbially degraded before styrene.

Structure/Activity Relationships: The International Agency for Research on Cancer (IARC, 1977) reported that there was insufficient evidence to support a determination of carcinogenicity in animals for hydroquinone, resorcinol or catechol. Subsequently, the National Toxicology Program (NTP) tested hydroquinone in a 2 year feeding study in rats and mice, reporting that this chemical showed some evidence of carcinogenicity in male and female rats (Ward *et al.*, 1991). The National Cancer Institute (NCI) has nominated catechol to the NTP for chronic carcinogenicity studies, and t-butylhydroquinone is currently being evaluated in a 2 year feeding study in rats and mice.

Deichmann and Keplinger (1981) reported a lack of specific evidence linking human cancer to phenolic compounds but stressed that evidence of carcinogenicity in mice dictates caution when handling these chemicals. In reviewing structural relationships of phenolic compounds to tumor formation, they postulated that the papilloma-promoting activity of phenol was reduced by the addition of a second phenolic hydroxy group and, further, that an unsubstituted position ortho to a phenolic hydroxy group seemed necessary for this

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papilloma-promoting activity. On the other hand, McGregor *et al.* (1988) found that while phenol was non-mutagenic in a mouse lymphoma cell L5178Y mutation assay, the addition of a second hydroxy group to the benzene ring resulted in mutagenic activity for all three dihydroxybenzene isomers. Catechol and hydroquinone demonstrated similar mutagenicity while resorcinol was a weaker mutagen. The acidic substituted catechols, 3,4-dihydroxycinnamic acid and 3,4-dihydroxybenzoic acid, were mutagenic as well as the neutral TBC which, along with catechol and hydroquinone, showed activity at the lowest dose level (see Table 3). L-Dopa and dopamine (analogs which are also substrates of tyrosinase) and other structurally related catecholamines were also found to be mutagenic in the L5178Y mouse lymphoma assay (McGregor *et al.*, 1988).

Based on an *in vitro* study of 4-alkylcatechols, including TBC, Furukawa *et al.* (1990) postulated that the potent stimulatory effect on nerve growth factor (NGF) demonstrated by these lipophilic compounds intracellularly required the presence of the two phenolic hydroxy groups. While p-*tert*-butylcatechol and catechol both enhanced rat stomach carcinogenesis, according to Hirose *et al.* (1989), 3-methylcatechol did not. The more lipophilic TBC demonstrated weaker promoting activity than catechol its more water-soluble parent.

The authors concluded that the presence of the two hydroxy groups on the benzene ring ortho to each other is important to the promotional activity or carcinogenic potential of these compounds in the glandular and/or fore-stomach. Another observation by these researchers was that analog, p-methylcatechol, induced moderately severe hyperplasia in all 15 rats that received it alone (i.e., not in conjunction with MNNG administration), as did TBC. In a parallel test system, other analogs (3-methylcatechol, hydroquinone and resorcinol) induced a less pronounced degree of hyperplasia. In addition, catechol, when administered at 0.25%, produced hepatic cell hyperplasia in a rat oral subchronic study. Finally, Hirose *et al.* (1988) reported that analogs, caffeic acid and BHA were weak carcinogens in rat forestomach epithelium; BHT was negative in this study.

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Table 3. Mutagenic potencies of some phenolic derivatives on the basis of their lowest observed effective dose (according to McGregor *et al.* (1988)

Lowest observed effective dose	Chemical
<10 g/ml	*tert*-Butyl catechol Catechol Hydroquinone
10-100 g/ml	3,4-Dihydroxybenzylamine Dopamine L-dopa Epinephrine
100-1,000 g/ml	Arterenol 3,4-Dihydroxyhydrocinnamic acid Resorcinol
>1,000 g/ml	3,4-Dihydroxybenzoic acid
Probably nonmutagenic[a]	Benzylamine Ephedrine Phenol Synephrine Tyramine

[a]Supplementary activation systems not used.

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