Pyrogallol
[87-66-1]

Review of Toxicological Literature

Prepared for

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EXECUTIVE SUMMARY

The nomination by Drs. Gold, Ames, and Slone, University of California, Berkeley, of pyrogallol for testing is based on its frequent occurrence in natural and manufactured products, including hair dyes, and the apparent lack of carcinogenicity data.

Pyrogallol (1,2,3-trihydroxybenzene) for commercial use is available from a number of U.S. producers, although information on production and import volumes was not located. It is primarily used as a modifier in oxidation dyes, including hair dyes and colors. Pyrogallol is also used as a developer in photography and holography; a mordant for dying wool; a chemical reagent for antimony and bismuth; and as an active reducer for gold, silver, and mercury salts. It is used for process engraving and for making colloidal solutions of metals. Additionally, pyrogallol is used in the manufacture of pharmaceuticals and pesticides and has been used for medicinal purposes as a topical antipsoriatic.

Workers in the dye and chemical industries, as well as those involved in textile and fur dying operations, may be potentially exposed to pyrogallol in the workplace. Photographers and holographers are potentially exposed during the developing process. Human exposure also occurs from the use of products containing pyrogallol as an ingredient. Hair coloring formulations containing pyrogallol may be applied to or come in contact with skin (particularly the scalp) and eyes. Pyrogallol may be ingested during the consumption of tea, water, smoked fish, or meat products containing pyrogallol. Inhalation of pyrogallol occurs from smoking tobacco products.

Pyrogallol may be released into the environment during its manufacture, transport, disposal, and industrial use. Pyrogallol is a byproduct of the decomposition of humic substances, and may be present in the water supply of geographic regions rich in organic matter, such as coals and shales. As a degradation product of quinic acid, pyrogallol is present in the wastes generated by the instant coffee making process.

U.S. Food and Drug Administration (FDA) regulations allow for the use of pyrogallol as a color additive. Pyrogallol may also be used in combination with ferric ammonium citrate for coloring catgut sutures for use in general and ophthalmic surgery.

In humans, ingestion of pyrogallol may cause gastrointestinal tract irritation, hemolysis, methemoglobinemia, renal injury, uremia, and death. One case of poisoning and death was reported from percutaneous absorption of an estimated 10 g (79 mmol) of pyrogallol (a dose of 143 mg/kg [1.13 mmol/kg] based on a 70-kg body weight). Chronic application of a topical cream containing pyrogallol resulted in the formation of ulcerated lesions on the hands of one psoriatic individual. In studies of contact sensitization using dermal occlusive patches, sensitization to pyrogallol was uncommon.

After dosing rats with pyrogallol by gavage or intraperitoneal (i.p.) injection, unchanged pyrogallol, 2-*O*-methylpyrogallol, and resorcinol (1,3-dihydroxybenzene) were detected in the urine. In mice treated i.p., pyrogallol concentrations peaked in the brain

within ten minutes and cleared within 15 minutes. In rats, intraventricular administration of pyrogallol resulted in the formation in the brain of three esters of pyrogallol.

Due to its activity as a catechol-*O*-methyltransferase (COMT) inhibitor, the effects of pyrogallol on the metabolism of catecholamines were investigated in mice, rats, and rabbits. Pyrogallol induced a transient rise followed by a fall in brain catecholamines; this response was caused by an initial inhibition of COMT followed by a feedback inhibition in catecholamine synthesis.

The acute oral LD_{50} for pyrogallol is 738 to 1800 mg/kg (5.85-14.3 mmol/kg) for rats, 1600 mg/kg (13 mmol/kg) for rabbits, 25 mg/kg (0.20 mmol/kg) for dogs, and 75 mg/kg (0.595 mmol/kg) for redwing blackbirds. The subcutaneous (s.c.) LD_{50} for pyrogallol is 700 mg/kg (5.6 mmol/kg) for rats.

When mice were treated acutely with pyrogallol by i.p. injection, only near lethal doses caused convulsions, which were accompanied by distinct cyanosis and occurred only after a sustained period of central nervous system depression; another study found that pyrogallol induced somnolence in mice. In rats, pyrogallol induced the Shwartzman reaction when given s.c. before bacterial endotoxin. The Shwartzman reaction is characterized by widespread hemorrhages, bilateral cortical necrosis of the kidneys, and a marked fall in leukocyte and platelet counts. Similarly, some rabbits treated orally with large doses of pyrogallol exhibited one or more of the following effects: congestion of the lung and liver, congestion and enlargement of the kidneys and spleen, and gastritis with hemorrhages and/or ulcers. In shrews, i.p. dosing with pyrogallol induced vomiting. Dermal application to the shaven skin of guinea pigs and rabbits was found to be slightly irritating, and ocular application was irritating to the eyes of rabbits. An analgesic action was noted upon intravenous (i.v.) administration of pyrogallol to rabbits.

One of two short-term dermal studies found that repeated pyrogallol treatment sensitized the skin of guinea pigs. In rabbits, however, dermal application of a hair dye formulation containing pyrogallol for 13 weeks did not induce toxic symptoms or gross or microscopic anomalies. Administration of pyrogallol in the diet in combination with sodium nitrite in drinking water for 4 weeks induced cell proliferation of the forestomach in rats. Feeding pyrogallol in the diet for 20 weeks induced mild hyperplasia of the forestomach in hamsters. The repeated oral LD_{50}, based on a 10-day study, for pyrogallol was 700 mg/kg/day for rabbits; symptoms were essentially the same as those experienced by rabbits administered acute oral doses. In cattle, oral administration of pyrogallol to three animals for up to six days induced symptoms of poisoning in all treated animals; one of these animals subsequently died.

Lifetime dermal exposure of mice and rabbits to low doses of pyrogallol did not induce toxic effects.

Pyrogallol induced few adverse reproductive effects in rats. An oral dose of pyrogallol on days 6 through 15 of gestation induced a decrease in fetal body weights and an

increase in the number of resorptions, but gross, visceral, or skeletal anomalies were not induced. Two dermal studies did not identify adverse effects from treatment of pregnant rats.

Lifetime dermal exposure of mice to pyrogallol was not carcinogenic. Similarly, oral administration of pyrogallol for 22 weeks did not induce bladder papillomas in rats. However, 58-week exposure of rats to pyrogallol by s.c. injection resulted in histiocytomas at the injection sites, and lifetime exposure to pyrogallol applied to the interior of the ear induced uterine tumors in 1 out of 5 treated rabbits at the highest dose tested.

In a dermal study, pyrogallol acted as a potent cocarcinogen by significantly increasing benzo[*a*]pyrene (B*a*P)-induced squamous cell carcinomas in mice. In a study using rats, however, pyrogallol did not act as a promotor of forestomach papillomas; pyrogallol was administered in the diet for 22 weeks after feeding *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (BBN) for two weeks.

Pyrogallol did not significantly inhibit *ß*-propiolactone (BPL)-induced neoplasia of the forestomach in mice.

In vitro, pyrogallol induced double strand breaks in purified λ phage DNA and in pBR322 plasmid DNA. In calf thymus DNA, pyrogallol induced DNA breakage in the presence, but not in the absence, of Cu^{2+}. In many studies, pyrogallol was reported to be mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, TA104, and TA1537 in the presence and absence of metabolic activation; and TA102 in the absence, but not the presence, of metabolic activation. However, pyrogallol was also reported to be nonmutagenic in *S. typhimurium* strains TA98, TA100, and TA1537 in the presence or absence of metabolic activation. Pyrogallol was not mutagenic in *S. typhimurium* strains TA1535 and TA1538 in the presence or absence of metabolic activation. Pyrogallol induced colicin E2 in *S. typhimurium* strain REN and expression of the *umu* gene in *S. typhimurium* strain 1535/pSK1002. In *Saccharomyces cerevisiae* strain D7, pyrogallol induced gene conversion when tested at pH 10, but not at pH 7. Pyrogallol induced sex-linked recessive lethal mutations in *Drosophila melanogaster* strains Berlin K and Basc.

Pyrogallol was shown to induce chromosome aberrations in Chinese hamster ovary (CHO) cells in the presence and absence of metabolic activation. Also in CHO cells, pyrogallol induced chromosome aberrations in the presence of Mn^{2+}, but not in the presence of Cu^{2+} (information on the presence/absence of metabolic activation not provided). Pyrogallol also induced chromosome aberrations in cultured human lymphocytes; micronuclei and sister chromatid exchanges (SCEs) in Chinese hamster V79 cells; and mutations in L5178Y mouse lymphoma cells. In *in vivo* mammalian systems, pyrogallol induced an increase in the frequency of micronucleated polychromatic erythrocytes (MN-PCE) and chromatid breaks in bone marrow cells of mice treated i.p.

When pBR322 plasmid DNA was incubated with pyrogallol in combination with a nitric oxide-releasing compound, a synergistic increase in DNA single strand breaks was induced. In *S. cerevisiae*, low concentrations of pyrogallol enhanced the mutagenic and

recombinogenic effect of triethylene melamine (TEM); at high concentrations, pyrogallol was still comutagenic but antirecombinogenic.

Pyrogallol inhibited B*a*P-induced mutagenicity in *S. typhimurium* strain TA98 in two studies; in one of the studies, the toxicity of pyrogallol to cells was not evaluated, but in the second study, pyrogallol inhibited B*a*P-induced mutagenicity at non-toxic doses. Pyrogallol was antigenotoxic in three experiments using mammalian systems *in vitro*; it inhibited B*a*P-induced mutagenicity in Chinese hamster V70 [*sic*] somatic cells, bovine papillomavirus-induced chromosome instability in C127 mouse mammary epithelial cells, and mitomycin C-induced chromosomal aberrations in CHO cells. *In vivo*, pyrogallol inhibited B*a*P-induced MN-PCE in the bone marrow of treated mice.

In two studies, pyrogallol was immunotoxic; it inhibited carrageenin-induced edema in rats *in vivo* and exhibited an immunosuppressive effect in mouse lymphocytes *in vitro*. Pyrogallol did not inhibit 1-fluoro-2,4-dinitrobenzene-induced contact hypersensitivity.

Pyrogallol inhibited formation of mutagenic nitrosation products of secondary amines and amides *in vitro*. Pyrogallol induced c-*fos* and c-*jun* protooncogene expression in human hepatoma HepG2 cells. Additionally, pyrogallol inhibited several enzymes, including COMT, rat liver aldehyde dehydrogenase, human melanoma tyrosinase, ribonucleotide reductase, hog thyroid peroxidase, and human splenic protein tyrosine kinase. Pyrogallol exhibited co-oxidase activity when tested with human liver lipoxygenase *in vitro*.

The order of clastogenic potential of hydroxylated phenols is trihydroxylated phenols (including pyrogallol) > dihydroxylated phenols > monohydroxylated phenols. The presence of a methyl ether derivative reduced the clastogenic capability of hydroxylated phenols. The inhibition of B*a*P-induced mutagenicity by polyhydric phenols follows the same potency pattern. One study found a correlation between the presence of a pyrogallol moiety in some naturally occurring compounds and their ability to inhibit UV-induced mutations in *E. coli*, but the mechanism of action was not determined.

TABLE OF CONTENTS

TABLES

ABBREVIATIONS

B*a*P	benzo[*a*]pyrene
BBN	*N*-butyl-*N*-(4-hydroxybutyl)nitrosamine
BPL	ß-propiolactone
CHO	Chinese hamster ovary
COMT	catechol-*O*-methyltransferase
i.p.	intraperitoneal injection
i.v.	intravenous injection
MN-PCE	micronucleated polychromatic erythrocytes
p.o.	by mouth
s.c.	subcutaneous injection
SCEs	sister chromatid exchanges
TEM	triethylene melamine
UV	ultraviolet

1.0 BASIS FOR NOMINATION

Pyrogallol was nominated for testing by Drs. Gold, Ames, and Slone, University of California, Berkeley, based on its frequent occurrence in natural and manufactured products, including hair dyes, and the apparent lack of carcinogenicity data.

2.0 INTRODUCTION

Pyrogallol

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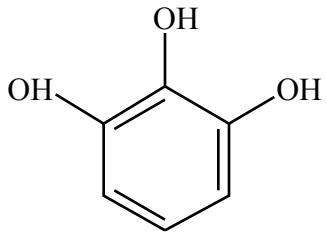

2.1 Chemical Identification

Pyrogallol ($C_6H_6O_3$; mol. wt. = 126.11) is also called:

1,2,3-benzenetriol
pyrogallic acid
1,2,3-trihydroxybenzene

2.2 Physical-Chemical Properties

Property	Information	Reference
Odor	odorless	Budavari (1996)
Physical State	white crystals; grayish on exposure to air and light	Budavari (1996)
Melting Point (^oC)	131-133	Budavari (1996)
Boiling Point (^oC)	309	Budavari (1996)
Density	1.45	Budavari (1996)
Soluble in:	water, alcohol, ether	Budavari (1996)
Slightly Soluble in:	benzene, chloroform, carbon disulfide	Budavari (1996)
Specific Gravity at 25^oC	1.45-1.50	CTFA (year not provided; cited by CIR, 1991)
Vapor Pressure	10 mm at 167.7^oC	Sax (1979; cited by CIR, 1991)
Conversion Factors	1 mg/L = 194 ppm 1 ppm (in air) = 5.15 mg/m^3	Clayton and Clayton (1981; cited by HSDB, 1996)

Iron and heavy metal impurities have been detected in pyrogallol (CTFA, year not provided; cited by CIR, 1991).

2.3 Commercial Availability

In the U.S., pyrogallol is commercially available from Aldrich Chemical Co., Eastman Organic Chemicals, Harshaw Chemical Co., Mallinckrodt, Inc. (HSDB, 1996), Penta Manufacturing Co., and Spectrum Bulk Chemicals (Rodnan, 1997).

3.0 PRODUCTION PROCESSES AND ANALYSES

For commercial purposes, pyrogallol is prepared from crude gallic acid, which is extracted from nutgalls or tara powder (Grayson, 1985). Pyrogallol may also be prepared by chlorinating cyclohexanol to form tetrachlorocyclohexanone, followed by hydrolysis (CTFA, year not provided; cited by CIR, 1991.

4.0 PRODUCTION AND IMPORT VOLUMES

Pyrogallol is produced in the U.S. by AgrEvo USA Co. and Mallinckrodt Baker, Inc. (SRI Int., 1997). However, information on production and import volumes for pyrogallol were not found.

5.0 USES

Pyrogallol was the first synthetic organic dye used on human hair; the color created by pyrogallol application was not provided (CIR, 1991). Currently, pyrogallol is used as a modifier in oxidation dyes (CTFA, year not provided; cited by CIR, 1991). Pyrogallol is present in 42 hair dyes and colors (FDA, 1989; cited by CIR, 1991) and the pyrogallol concentration in the dyes and colors typically ranges from 0.25 to 0.38% by weight (Clayton and Clayton, 1981; cited by CIR, 1991).

Pyrogallol is also used for dying fur and wool, staining leather, and manufacturing various dyes (Budavari, 1996). Pyrogallol is used in combination with ferric ammonium citrate to color

catgut sutures used in general and ophthalmic surgery (21 CFR 73.1375).

Pyrogallol is used as a developer in photography (Budavari, 1996) and holography (McCann, 1992); a chemical reagent for antimony and bismuth; and as an active reducer for gold, silver, and mercury salts (Budavari, 1996). It is used for making colloidal solutions of metals, process engraving (Nor-Am Chemical Co., 1985; cited by CIR, 1991), and in the manufacture of pharmaceuticals and pesticides (Grayson, 1985). Due to its antioxidant properties, pyrogallol is used as a corrosion inhibitor (i.e., oxygen scavenger) in boilers (Zupanovich et al., 1985; Rossi and Burgmayer, 1991). Additionally, pyrogallol is used as "an oxygen scrubbing solution" for producing high purity nitrogen used in the Monier-Williams Procedure for determining sulfites in food (21 CFR 101.108).

Medically, pyrogallol has been used as a topical antipsoriatic (Budavari, 1996). It was typically applied in an ointment containing 2 to 10% pyrogallol (Stecher, 1968). In Australia, pyrogallol has been used as a topical therapy for chronic plaque psoriasis since the beginning of the century (Pweny, 1925; cited by Willsteed and Regan, 1985), but usage has declined since the 1960s (Willsteed and Regan, 1985). In Europe in the 1970s, pyrogallol was used in conjunction with ultraviolet B for the treatment of resistant psoriasis (Siage, 1976; Meffert, 1970; cited by Willsteed and Regan, 1985).

6.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE

In nature, pyrogallol is incorporated in tannins, anthocyanins, flavones, and alkaloids (Grayson, 1985).

Pyrogallol may be released into the environment during its manufacture, transport, disposal, and industrial use. Pyrogallol is a byproduct of the decomposition of humic substances, and may be present in the water supply of geographic regions rich in organic matter such as coals and shales (Cooksey et al., 1985). Resorcinol (1,3-benzenediol; a metabolite of pyrogallol in rats) and other phenolic compounds are abundant thermal breakdown products in wastewater effluents of coal-conversion processes (Jahnig and Bertrand, 1976; Pitt et al., 1979; Klibanov et al., 1983; all cited by Cooksey et al., 1985).

As a degradation product of quinic acid (1*R*-(1α,3α,4α,5ß)]-1,3,4,5-tetrahydroxycyclohexanecarboxylic acid), pyrogallol is present in the wastes generated by the instant coffee making process (Azhar and Stuckey, 1994). Only 54% of the pyrogallol formed was degraded by anaerobic digestion.

7.0 HUMAN EXPOSURE

Workers in the dye (particularly hair dyes) and chemical industries, as well as those working in dying operations in the textile and fur industries, may potentially be occupationally exposed to pyrogallol. Photographers (Miller and Blair, 1983) and holographers are potentially exposed to pyrogallol in the developing process (McCann, 1992).

Hair coloring formulations containing pyrogallol are applied to or may come in contact with hair, skin (particularly the scalp), eyes, and nails (CIR, 1991). These formulations may be used on a weekly basis.

Ingestion of pyrogallol occurs from consumption of tea (Aeschbacher, 1991) and water derived from aquifers and/or wells in regions containing high quantities of coal and shale (Cooksey et al., 1985). Pyrogallol exposure also occurs from the ingestion of smoke condensates present in smoked fish and meat products (Ohshima et al., 1989). Inhalation of pyrogallol occurs from smoking tobacco products (Pettersson et al., 1982).

8.0 REGULATORY STATUS

Under 21 CFR 73.1375, the Food and Drug Administration (FDA) listed pyrogallol as exempt from certification as a color additive. 21 CFR 73.1025 states that "ferric ammonium citrate may be safely used in combination with pyrogallol for coloring plain and chromic catgut sutures for use in general and ophthalmic surgery."

9.0 TOXICOLOGICAL DATA

Summary: In humans, ingestion of pyrogallol may cause gastrointestinal tract irritation, hemolysis, methemoglobinemia, renal injury, uremia, and death. One case of

poisoning and death was reported from percutaneous absorption of an estimated 10 g (79 mmol) of pyrogallol (a dose of 143 mg/kg [1.13 mmol/kg] based on a 70-kg body weight). Chronic application of a topical cream containing pyrogallol resulted in the formation of ulcerated lesions on the hands of one psoriatic individual. In studies of contact sensitization using dermal occlusive patches, sensitization to pyrogallol was uncommon.

After dosing rats with pyrogallol by gavage or i.p. injection, unchanged pyrogallol, 2-*O*-methylpyrogallol, and resorcinol (1,3-dihydroxybenzene) were detected in the urine. In mice treated i.p., pyrogallol concentrations peaked in the brain within ten minutes and cleared within 15 minutes. In rats, intraventricular administration of pyrogallol resulted in the formation of three esters of pyrogallol in the brain.

Due to its activity as a COMT inhibitor, the effects of pyrogallol on the metabolism of catecholamines were investigated in mice, rats, and rabbits. Pyrogallol induced a transient rise followed by a fall in brain catecholamines; this response was caused by an initial inhibition of COMT followed by a feedback inhibition in catecholamine synthesis.

The acute oral LD_{50} for pyrogallol is 738 to 1800 mg/kg (5.85-14.3 mmol/kg) for rats, 1600 mg/kg (13 mmol/kg) for rabbits, 25 mg/kg (0.20 mmol/kg) for dogs, and 75 mg/kg (0.595 mmol/kg) for redwing blackbirds. The s.c. LD_{50} for pyrogallol is 700 mg/kg (5.6 mmol/kg) for rats.

When mice were treated acutely with pyrogallol by i.p. injection, only near lethal doses caused convulsions, which were accompanied by distinct cyanosis and occurred only after a sustained period of central nervous system depression. Another study found that pyrogallol induced somnolence in mice. In rats, pyrogallol induced the Shwartzman reaction when given s.c. before bacterial endotoxin. Similarly, some rabbits treated orally with large doses of pyrogallol exhibited one or more of the following effects: congestion of the lungs and liver, congestion and enlargement of the kidneys and spleen, and gastritis with hemorrhages and/or ulcers. In shrews, i.p. dosing with pyrogallol induced vomiting. Dermal application to the shaven skin of guinea pigs and rabbits was found to be slightly irritating, and ocular application was irritating to the eyes of rabbits. An analgesic action was noted upon i.v. administration of pyrogallol to rabbits.

One of two short-term dermal studies found that repeated pyrogallol treatment sensitized the skin of guinea pigs. In rabbits, however, dermal application of a hair dye formulation containing pyrogallol for 13 weeks did not induce toxic symptoms or gross or microscopic anomalies. Administration of pyrogallol in the diet in combination with sodium nitrite in the drinking water for 4 weeks induced cell proliferation of the forestomach in rats, while feeding pyrogallol in the diet for 20 weeks induced mild hyperplasia of the forestomach in hamsters. The repeated oral LD_{50}, based on a 10-day

study, for pyrogallol was 700 mg/kg/day for rabbits; symptoms were essentially the same as those experienced by rabbits administered acute oral doses. In cattle, oral administration of pyrogallol to three animals for up to six days induced symptoms of poisoning in all treated animals; one of these animals subsequently died.

Lifetime dermal exposure of mice and rabbits to low doses of pyrogallol did not induce toxic effects.

Pyrogallol induced few adverse reproductive effects in rats. An oral dose of pyrogallol on days 6 through 15 of gestation induced a decrease in fetal body weights and an increase in the number of resorptions, but gross, visceral, or skeletal anomalies were not induced. Two dermal studies did not identify adverse effects from treatment of pregnant rats.

Lifetime dermal exposure of mice to pyrogallol was not carcinogenic. Similarly, oral administration of pyrogallol for 22 weeks did not induce bladder papillomas in rats. However, 58-week exposure of rats to pyrogallol by s.c. injection resulted in histiocytomas at the injection sites, and lifetime exposure to pyrogallol applied to the interior of the ear induced uterine tumors in 1 out of 5 treated rabbits at the highest dose tested.

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Pyrogallol did not significantly inhibit BPL-induced neoplasia of the forestomach in mice.

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Pyrogallol inhibited B*a*P-induced mutagenicity in *S. typhimurium* strain TA98 in two studies; in one of the studies, the toxicity of pyrogallol to cells was not evaluated, but in the second study, pyrogallol inhibited B*a*P-induced mutagenicity at non-toxic doses. Pyrogallol was antigenotoxic in three experiments using mammalian systems *in vitro*; it inhibited B*a*P-induced mutagenicity in Chinese hamster V70 [*sic*] somatic cells, bovine papillomavirus-induced chromosome instability in C127 mouse mammary epithelial cells, and mitomycin C-induced chromosomal aberrations in CHO cells. *In vivo*, pyrogallol inhibited B*a*P-induced MN-PCE in the bone marrow of treated mice.

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Pyrogallol inhibited the formation of mutagenic nitrosation products of secondary amines and amides *in vitro*. Pyrogallol induced c-*fos* and c-*jun* protooncogene expression in human hepatoma HepG2 cells. Additionally, pyrogallol inhibited several enzymes, including COMT, rat liver aldehyde dehydrogenase, human melanoma tyrosinase, ribonucleotide reductase, hog thyroid peroxidase, and human splenic protein tyrosine kinase. Pyrogallol exhibited co-oxidase activity when tested with human liver lipoxygenase *in vitro*.

The order of clastogenic potential of hydroxylated phenols is trihydroxylated phenols (including pyrogallol) > dihydroxylated phenols > monohydroxylated phenols. The presence of a methyl ether derivative reduced the clastogenic capability of hydroxylated phenols. The inhibition of B*a*P-induced mutagenicity by polyhydric phenols follows the same potency pattern. One study found a correlation between the presence of a pyrogallol moiety in some naturally occurring compounds and their ability to inhibit UV-induced mutations in *E. coli*, but the mechanism of action was not determined.

9.1 General Toxicology

9.1.1 Human Data

Ingestion of pyrogallol (dose not provided) may cause gastrointestinal tract irritation, hemolysis, methemoglobinemia, renal injury, uremia, and ultimately death (Gosselin et al., 1981). Poisoning and death have also occurred from percutaneous absorption. Pyrogallol is mildly caustic to skin and mucous membranes.

9.1.1.1 Experimental Studies

Pyrogallol was tested for sensitization in eight individuals found to be sensitive to resorcinol (a metabolite of pyrogallol) in eyedrops, creams, or other medicinal preparations (Keil, 1962). Five of those individuals were mildly sensitized by treatment with 2% (159 mM) pyrogallol in alcohol by occlusive patch. The length of pyrogallol exposure was not provided.

In a 15-year study of various cosmetic ingredients, 8230 patients with allergic contact dermatitis were treated with 1% (79 mM) pyrogallol by occlusive patch (Angelini et al., 1985; cited by CIR, 1991). No positive skin reactions to pyrogallol were reported.

When 25 patients with leg ulcers that had persisted for 12 months or more were treated with pyrogallol (dose not provided) by occlusive patch, skin sensitization reactions to pyrogallol were observed in 3 patients (12%) (Kokelj and Cantarutti, 1986).

Three studies investigated the ability of pyrogallol to induce skin sensitization in hairdressers and their customers who had contact dermatitis. The volunteers were administered 1% (79 mM) pyrogallol in petrolatum by occlusive patch for two to three days. In one study of 302 hairdressers, 1.3% (4 individuals) had positive skin sensitization to the treatment (Guerra et al., 1992a). In another study of 261 customers of hairdressers, 2.6% (6 individuals) experienced sensitization reactions (Guerra et al., 1992b). In a third study of 781 hairdressers, 0.76% (6 individuals) experienced positive sensitization reactions (Frosch et al., 1993).

9.1.1.2 Case Reports

A psoriatic patient who covered two-thirds of his body with an ointment containing

pyrogallol collapsed within 5 minutes postapplication and died in a coma 24 hours later (Gosselin et al., 1981). The man absorbed an estimated 10 g (79 mmol) of pyrogallol, which corresponds to a 143 mg/kg (1.13 mmol/kg) dose based on a 70-kg body weight.

To treat psoriasis, one Australian man applied an aqueous cream containing 10% (793 mM) pyrogallol to his hands nearly every morning for 40 years (Willsteed and Regan, 1985). After applying the cream, the man wore white gloves for the remainder of the day. At the age of 77, the man presented himself to the hospital with 3 ulcerated lesions on the dorsa of his hand; the lesions had been slowly enlarging over the previous 18 months. The authors stated that these cutaneous malignancies were "almost certainly related to the prolonged topical exposure to [pyrogallol]." The patient indicated no history of exposure to other substances and the gloves provided 40 years of protection from solar radiation. The patient did not have cutaneous neoplasms on other parts of his body.

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

9.1.2.1 Absorption, Distribution, Metabolism, and Excretion

When pyrogallol was administered by gavage or i.p. injection to albino rats (sex not provided) at 100 mg/kg (0.79 mmol/kg), unchanged pyrogallol, 2-*O*-methylpyrogallol, and traces of resorcinol were detected in the urine (Scheline, 1966; cited by CIR, 1991). *In vitro*, intestinal microflora of these rats metabolized pyrogallol to resorcinol by dehydroxylation (Scheline, 1966; cited by CIR, 1991; Scheline, 1968).

When pyrogallol at 100 mg /kg (0.79 mmol/kg) was administered to male albino rats by gavage, 6.2% of the dose was excreted in the urine as 2-*O*-methyl-pyrogallol 48 hours after dosing (Bakke, 1970).

The maximum concentration of pyrogallol in the brains of male mice (strain not provided) administered 120 mg pyrogallol/kg (0.951 mmol/kg) i.p. was observed 10 minutes after the injection (Rogers et al., 1968). These results were confirmed by i.p. administration of 60 mg pyrogallol/kg (0.48 mmol/kg) to female mice (strain not provided) (Angel et al., 1969; cited by CIR, 1991); within 15 minutes postinjection, the brain concentration of pyrogallol was near zero.

A 2 mg (0.02 mmol) intraventricular dose of pyrogallol administered to male Wistar rats resulted in the formation in the brain of three unidentified esters of pyrogallol (Eccleston and Ritchie, 1973).

9.1.2.2 Effects on the Metabolism of Catecholamines

A 10 mg/kg (0.079 mmol/kg) dose of pyrogallol increased catecholamines in various regions of the brain in mice and rats (sex and strain not provided) within 20 to 40 minutes after a single i.p. injection (Izquierdo et al., 1964; cited by Guldberg and Marsden, 1975). It increased the levels of catecholamines in the brain of a rabbit within one hour after intracisternal injection (Matsouka et al., 1962; cited by Guldberg and Marsden, 1975).

However, pyrogallol did not elevate the level of catecholamines in the brain of rats (sex and strain not provided) after repeated i.p. dosing with 50 mg/kg (0.40 mmol/kg) every 30 minutes for 18 hours (Crout et al., 1961; cited by Guldberg and Marsden, 1975) or after daily administration (dose not provided) for several weeks (Maitre, 1966; cited by Guldberg and Marsden, 1975). Treatment with pyrogallol (12 or 50 mg/kg [0.095 or 0.40 mmol/kg] every 30 minutes) induced a significant decrease in brain norepinephrine (Crout et al., 1961; cited by Guldberg and Marsden, 1975). Guldberg and Marsden (1975) explained the transient rise followed by a fall in brain catecholamines after pyrogallol treatment as being caused by an initial inhibition of COMT followed by a feedback inhibition in catecholamine synthesis.

9.1.3 Acute Exposure

Acute toxicity values are presented in **Table 1**. Acute exposure studies discussed in this section are presented in detail in **Table 2**.

Table 1. Acute Toxicity Values for Pyrogallol

Species (sex and strain)	Route	LD_{50}	Reference
rat (male, Sprague-Dawley)	oral	1800 mg/kg (14.3 mmol/kg)	Clairol (1981; cited by CIR, 1991)
		1255 mg/kg (9.95 mmol/kg)	Sharp and Saunders (1984a; cited by CIR, 1991)
		1171 mg/kg (9.29 mmol/kg)	
rat (female, Sprague-Dawley)	oral	838 mg/kg (6.64 mmol/kg)	Sharp and Saunders (1984a; cited by CIR, 1991)
		738 mg/kg (5.85 mmol/kg)	
rat (sex and strain n.p.)	s.c.	700 mg/kg (5.6 mmol/kg)	Stecher (1968)
rabbit (sex and strain n.p.)	oral	1600 mg/kg (13 mmol/kg)	Dollahite et al. (1962)
dog (sex and strain n.p.)	oral	25 mg/kg (0.20 mmol/kg)	Stecher (1968)
redwing blackbird (sex and strain n.p.)	oral	75.0 mg/kg (0.595 mmol/kg)	Schafer et al. (1983)

Abbreviations: s.c. = subcutaneous injection; n.p. = not provided

9.1.3.1 Mice

Several studies investigated the effects of i.p. administration of pyrogallol to mice. Although pyrogallol is an inhibitor of COMT, a 120 mg/kg (0.95 mmol/kg) dose of pyrogallol did not alter motor activity and did not change the levels of norepinephrine, dopamine, or 5-hydroxytryptamine in the mouse brain (Rogers et al., 1968). Based on the findings of Angel and Rogers (1968), Rogers et al. (1968) stated that only near-lethal doses (lethal dose not provided) induced convulsions in mice; the dose inducing convulsions in 50% of the animals (CD_{50}) was 720 mg/kg (5.71 mmol/kg) (Angel and Rogers, 1968). Convulsions were accompanied by distinct cyanosis and occurred only after a sustained period of central nervous system depression. The authors attributed the convulsions to anoxia rather than COMT inhibition. A later study by Angel and Rogers (1972) found that pyrogallol treatment induced somnolence instead of convulsions; the administered doses were not provided.

Table 2. Acute Exposure to Pyrogallol

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
9.1.3.1 Mice						
mice (inbred, age n.p.)	10 M	pyrogallol, purity n.p.	120 mg/kg (0.951 mmol/kg) i.p.	single exposure; observed for 30 min.	Treatment did not alter motor activity and did not change the levels of norepinephrine, dopamine, or 5-hydroxytryptamine in the brain.	Rogers et al. (1968)
mice (inbred strain, age n.p.)	10 F per dose	pyrogallol, purity n.p.	varying i.p. doses (n.p.)	single exposure; observation period n.p.	The dose inducing convulsions in 50% of the animals (CD_{50}) was 5.71 mmol/kg (720 mg/kg). Convulsions were accompanied by distinct cyanosis and occurred only after a sustained period of central nervous system depression. The authors stated that the convulsions may have been anoxic in origin and that the CNS effects of pyrogallol are unrelated to its inhibition of COMT.	Angel and Rogers (1968)
mice (Sheffield albino, age n.p.)	6 per dose (sex n.p.)	pyrogallol, purity n.p.	varying i.p. doses (n.p.) administered as a single compound or with *d*-amphetamine	single exposure; observation period n.p.	Pyrogallol treatment induced somnolence instead of convulsions. Pyrogallol also diminished the excitatory effect of *d*-amphetamine on locomotor activity.	Angel and Rogers (1972)
mice (Swiss-Webster, 6-10 wk-old)	2 M	pyrogallol, purity n.p.	400 mg/kg (3.17 mmol/kg) i.p.	single exposure; observed 4 days later	Body and lung weights were not affected by treatment.	Malkinson (1979)
rats (albino, 5-6 mo-old)	5 M	pyrogallol , chromatographically pure	100 mg/kg (0.793 mmol/kg) by gavage	single exposure; 48-hour observation period	No symptoms of motor disturbances were observed.	Bakke (1970)
9.1.3.2 Rats						

Abbreviations: CNS = central nervous system; COMT = catechol-*O*-methyl transferase; F = female; HD = high dose; 5-HT = 5-hydroxytryptamine$_3$; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid-dose; n.p. = not provided; s.c. = subcutaneous; *Suncus murinus* = house musk shrew

Table 2. Acute Exposure to Pyrogallol

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
rats (Holtzmann, age n.p.)	17 M	pyrogallol and bacterial endotoxin, purity n.p.	300 or 500 mg pyrogallol/kg (2.38 or 3.96 mmol/kg) s.c. followed in 15 min. by 1 mg endotoxin/kg	single exposure; observation period n.p.	The Boivin-type endotoxin from *Salmonella typhosa* strain 0901 was used. Treatment induced the generalized Shwartzman reaction. Pyrogallol enhanced the action of the endotoxin on the coagulation system, as was measured by increased consumption of the proconvertin (a coagulation factor), fibrinogen, and platelets. The authors concluded that interference with the degradation of circulating catecholamines results in sensitization to the generalized Shwartzman reaction. The generalized Shwartzman reaction is characterized by widespread hemorrhages, bilateral cortical necrosis of the kidneys, and a marked fall in leukocyte and platelet counts (Dorland's Illustrated Medical Dictionary, 1984). The reaction usually results in death of the animal.	Latour and Léger-Gauthier (1978)
rats (Sprague-Dawley, age n.p.)	≥4 M	pyrogallol, purity n.p.	250 mg/kg (1.98 mmol/kg) i.p. 1, 3.5, or 6 hours before ethanol	single exposure; 5-hour observation period	Pyrogallol dramatically increased acetaldehyde blood levels within 20 min. after ethanol administration.	Collins et al. (1974)

Table 2. Acute Exposure to Pyrogallol (continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
9.1.3.3 Shrews						
Suncus murinus (strain and age n.p.)	1 at the LD and 5 and the MD and HD (sex n.p.)	pyrogallol, purity n.p.	32, 64, or 128 mg/kg i.p. (0.25, 0.51, or 1.01 mmol/kg)	single exposure; observed for 90 min.	Treatment-induced vomiting was dose-dependent (0/1, LD; 1/5, MD, and 5/5 HD). The authors stated that the generation of free radicals by pyrogallol administration causes the release of peripheral 5-HT, which stimulates vagal afferent sensory nerves to cause emesis.	Torii et al. (1994)
9.1.3.4 Guinea Pigs						

Abbreviations: CNS = central nervous system; COMT = catechol-*O*-methyl transferase; F = female; HD = high dose; 5-HT = 5-hydroxytryptamine$_3$; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid-dose; n.p. = not provided; s.c. = subcutaneous; *Suncus murinus* = house musk shrew

Table 2. Acute Exposure to Pyrogallol (continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
guinea pigs (Dunkin Hartley, age n.p.)	6 F	pyrogallol (technical synthetic, 92.2% pure, w/w)	25 mg in solution applied to 2 sites on the back via patches Calculated pyrogallol dose: 23.1 mg/site (0.18 mmol/site)	exposure sites covered for 24 hours; observed 1, 4, 24, 48, and 72 hours after patch removal	Very slight erythema observed at 1 site (2 guinea pigs). 4 to 8 days after patch removal, dryness and thickening leading to flaking of the skin was observed at all treated sites except one. Technical synthetic pyrogallol classified as slightly irritating.	Sharp and Saunders (1984b; cited by CIR, 1991)
guinea pigs (Dunkin Hartley, age n.p.)	6 F	pyrogallol (technical natural, 98.8% pure, w/w)	25 mg in solution applied to 2 sites on the back via patches Calculated pyrogallol dose: 24.7 mg/site (0.20 mmol/site)	exposure sites covered for 24 hours; observed 1, 4, 24, 48, and 72 hours after patch removal	Very slight erythema observed at 1 site (3 guinea pigs). 4 to 8 days after patch removal, dryness and thickening leading to flaking of the skin was observed at all treated sites except one. Technical natural pyrogallol classified as slightly irritating.	Sharp and Saunders (1984b; cited by CIR, 1991)
9.1.3.5 Rabbits						
rabbits (strain and age n.p.)	6 (sex n.p.)	pyrogallol, reagent grade	750-2000 mg/kg (5.9-15.9 mmol/kg) by gavage	single exposure; observation period n.p.	The following symptoms were observed in some treated rabbits: congestion of the lung; congestion of the liver, with prominent lobules (alternate light and congested areas were observed); congestion and swelling of the kidneys; congestion and enlargement of the spleen; and gastritis, usually with hemorrhages and/or ulcers. The doses which caused these effects and the number of animals affected were n.p.	Dollahite et al. (1962)
rabbits (albino, age n.p.)	6 (sex n.p.)	pyrogallol, powder form, purity n.p.	500 mg (3.96 mmol) applied to abraded and intact skin	exposure sites covered for 24 hours; observed 24 and 72 hours after treatment	A primary irritation index of 0.5 was reported. The irritation index scoring range was n.p.	Clairol (1979; cited by CIR, 1991)
rabbits (white New Zealand, age n.p.)	6 M	pyrogallol, powder form, purity n.p.	100 mg (0.793 mmol) instilled in the conjunctival sac of the eye	single exposure; observation period n.p.	Ocular irritation was induced.	Clairol (1979; cited by CIR, 1991)
		pyrogallol, 1.0% solution in propylene glycol	0.1 mL instilled in the eye calculated pyrogallol dose: 1 mg (8 µmol))		No ocular irritation was observed.	
rabbits (strain n.p., adult)	n.p.	pyrogallol, purity n.p.	3 or 12 mg/kg (0.02 or 0.10 mmol/kg) i.v.	single exposure; observed for 45 min.	Using the rabbit tooth pulp assay, all doses significantly increased the nociceptive threshold (i.e., acted as an analgesic).	Gardella et al. (1970)

Abbreviations: CNS = central nervous system; COMT = catechol-*O*-methyl transferase; F = female; HD = high dose; 5-HT = 5-hydroxytryptamine$_3$; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid-dose; n.p. = not provided; s.c. = subcutaneous; *Suncus murinus* = house musk shrew

Table 2. Acute Exposure to Pyrogallol (continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
			0.1 or 0.2 mg/kg (0.0008 or 0.002 mmol/kg) by intraventricular injection			

Abbreviations: CNS = central nervous system; COMT = catechol-*O*-methyl transferase; F = female; HD = high dose; 5-HT = 5-hydroxytryptamine$_3$; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid-dose; n.p. = not provided; s.c. = subcutaneous; *Suncus murinus* = house musk shrew

A 400 mg/kg dose of pyrogallol administered i.p. did not affect the body and lung weights of mice (Malkinson, 1979).

9.1.3.2 Rats

Effects of pyrogallol on COMT inhibition were investigated in rats. A single p.o. pyrogallol dose of 100 mg/kg (0.793 mmol/kg) did not elicit symptoms of motor disturbances (Bakke, 1970). However, when pyrogallol (300 or 500 mg/kg; 2.38 or 3.96 mmol/kg) was given s.c. to rats 15 minutes before an i.v. injection of bacterial endotoxin, pyrogallol enhanced the action of the endotoxin on the coagulation system, thus inducing the generalized Shwartzman reaction (Latour and Léger-Gauthier, 1978). As a COMT inhibitor, pyrogallol interfered with the degradation of circulating catecholamines.

A 250 mg/kg (2 mmol/kg) i.p. injection of pyrogallol at 1, 3.5, or 6 hours before administering ethanol to rats dramatically increased the blood levels of acetaldehyde compared with alcohol administration alone (Collins et al., 1974). Because other COMT inhibitors did not induce the same response, the authors stated that a mechanism involving inhibition of COMT and subsequent competitive inhibition of aldehyde dehyrogenase was precluded. Stimulation of ethanol oxidation is presumably involved in the mechanism, since pyrogallol is suspected to be a potent H_2O_2-generating agent in aqueous solution.

9.1.3.3 Shrews

In *Suncus murinus*, i.p. pyrogallol (32, 64, or 128 mg/kg; 0.25, 0.51, or 1.01 mmol/kg) treatment induced vomiting in a dose-dependent manner (Torii et al., 1994). The authors stated that the generation of free radicals by pyrogallol causes the release of peripheral 5-hydroxytryptamine$_3$, which stimulated vagal afferent sensory nerves to cause emesis.

9.1.3.4 Guinea Pigs

Pyrogallol (23.1 or 24.7 mg/site; 0.18 or 0.20 mmol/site) was classified as slightly irritating to the skin based on a study using occlusive dermal patches applied to the backs of guinea pigs for 24 hours (Sharp and Saunders, 1984b; cited by CIR, 1991).

9.1.3.5 Rabbits

In a study designed to determine the oral LD_{50} dose for pyrogallol, rabbits were administered pyrogallol by gavage at 750 to 2000 mg/kg (5.9-15.9 mmol/kg) (Dollahite et al., 1962). Symptoms observed in some animals (number and dose level not provided) included congestion of the lungs, liver, kidneys, and spleen. The latter two organs were also enlarged. Gastritis with hemorrhages and/or ulcers were induced in some animals.

When pyrogallol was administered at 500 mg (3.96 mmol) by occlusive patch to either the abraded or intact skin of rabbits, a primary irritation index of 0.5 was reported (Clairol, 1979a; cited by CIR, 1991). The irritation index scoring range was not provided.

Pyrogallol, at 100 mg (0.793 mmol), induced ocular irritation in rabbits, but 1 mg (8 μmol) pyrogallol had no effect (Clairol, 1979a; cited by CIR, 1991).

Pyrogallol, administered by i.v. (3 or 12 mg/kg; 0.02 or 0.10 mmol/kg) or intraventricular injection (0.1 or 0.2 mg/kg; 0.0008 or 0.002 mmol/kg) significantly increased the nociceptive threshold when tested using the rabbit tooth pulp assay (Gardella et al., 1970). This analgesic response may be related to inhibition of COMT by pyrogallol, which allows for an increase in brain catecholamine concentrations.

9.1.4 Short-Term and Subchronic Exposure

The details of these studies are presented in **Table 3**.

9.1.4.1 Rats

In one study, 2% pyrogallol was administered to rats in the diet with 1% sodium ascorbate and/or sodium nitrite for 4 weeks (Yoshida et al., 1994). Pyrogallol with sodium nitrite

or with both sodium ascorbate in the diet and sodium nitrite in the drinking water statistically increased cell proliferation in the forestomach mucosa, but treatment with pyrogallol alone or in combination with sodium ascorbate had no effect (nitrosating agent was absent). The authors stated that the degree of such hyperplasia is well correlated with tumor promotion or tumorigenicity (correlation factor not provided) and that chronic treatment with pyrogallol plus sodium nitrite may induce forestomach tumors.

9.1.4.2 Hamsters

Feeding pyrogallol as 1% of the diet for 20 weeks induced mild hyperplasia of the forestomach in hamsters (Hirose et al., 1986).

9.1.4.3 Guinea Pigs

Mixed results were obtained from two studies investigating the skin sensitization potential of pyrogallol. In one study, treatment included injection of 0.05 mL of a 1% (80 mM) pyrogallol solution intradermally followed in one week by an application of a 25% (2 M) pyrogallol solution using a 48-hour occlusive patch (Clairol, 1979b; cited by CIR, 1991). No treatment was given for two weeks, and then a second application of a 25% pyrogallol was applied topically by occlusive patch. This treatment resulted in no skin sensitization.

Table 3. Short-Term and Subchronic Exposure to Pyrogallol

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
9.1.4.1 Rats						
rats (F344, 6-wk-old)	5 M per dose	pyrogallol, purity n.p.	2% in the diet	4-week exposure; sacrificed at the end of exposure	Pyrogallol treatment did not induce cell proliferation in forestomach mucosa.	Yoshida et al. (1994)
			2% pyrogallol in the diet plus 1% sodium ascorbate in the diet and/or 0.3% $NaNO_2$ in the drinking water		Pyrogallol administration with $NaNO_2$ with or without sodium ascorbate significantly increased the thickness of the forestomach mucosa (i.e., induced cell proliferation). Treatment with pyrogallol plus sodium ascorbate without $NaNO_2$ or $NaNO_2$ alone had no effect. The authors stated that induced hyperplasia is well correlated with tumor promotion or tumorigenicity (correlation factor n.p.) and that combined treatment with pyrogallol and $NaNO_2$ may result in forestomach tumors in the long term.	
9.1.4.2 Hamsters						
hamsters (Syrian golden, 7-wk-old)	15 M	pyrogallol, >98% pure	1% in the diet 3 animals were also given [methyl-^{3}H]thymidine i.p. one hour before sacrifice	20-week exposure; sacrificed at the end of exposure period	Treatment induced mild hyperplasia of the forestomach in all dosed hamsters, but the labeling index in the forestomach, glandular stomach, and urinary bladder epithelium was not statistically increased in the hamsters given [methyl-^{3}H]thymidine i.p.	Hirose et al. (1986)
9.1.4.3 Guinea Pigs						
guinea pigs (Hartley albino, age n.p.)	10 F	pyrogallol, purity n.p.	0.05 mL of a 1% (80 mM) solution injected intradermally; 1 week later a 25% (2 M) solution was applied topically under occlusion for 48 hours; after 2 weeks of nontreatment, a 2nd dose of 25% solution was applied topically	see dose for exposure period; observation period n.p.	No skin sensitization was observed.	Clairol (1979b; cited by CIR, 1991)

Abbreviations: F = female; M = male; $NaNO_2$ = sodium nitrite; n.p. = not provided; s.c. = subcutaneous

Table 3. Short-Term and Subchronic Exposure to Pyrogallol

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
guinea pigs (Hartley, age n.p.)	29 F	pyrogallol (unrefined, purity n.p.)	0.1 mL of 100 or 500 mM solution (0.01 or 0.05 mmol pyrogallol) s.c. on 3 consecutive days into the feet; in the same week, a 4th injection near the neck was administered. The challenge treatment 4 wk after initial injection was either a 5th s.c. injection (21 animals) or a sealed cloth application (8 animals)	see dose for exposure period; observation period n.p.	Of those animals receiving the s.c. challenge treatment, 7 and 14 animals had sensitization reactions to 0.01 M and 0.05 M pyrogallol, respectively. Of those animals receiving the challenge treatment as sealed cloth applications, 3 and 6 animals had sensitization reactions to 0.01 M and 0.05 M pyrogallol, respectively. Please note: The discrepancy between the number of animals reported to have sensitization reactions and the number of animals treated was present in the source paper.	Masamoto and Takase (1983; cited by CIR, 1991)

Table 3. Short-Term and Subchronic Exposure to Pyrogallol (continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
9.1.4.4 Rabbits						
rabbits (strain and age n.p.)	6 (sex n.p.)	pyrogallol, reagent grade	500-1000 mg/kg (4.0-7.93 mmol/kg) per day by gavage	10-day exposure; observation period n.p.	A repeated-dose LD_{50} of 700 mg/kg/day was determined. The following symptoms were observed in some treated rabbits: congestion of the lung; congestion of the liver, with prominent lobules (alternate light and congested areas were observed); congestion and swelling of the kidneys; congestion and enlargement of the spleen; and gastritis, usually with hemorrhages and/or ulcers. A smooth white exudate was induced on the gastric mucosa and there was a varying degree of enteritis in the duodenum and cecum. The doses which caused these effects and the number of animals affected were n.p.	Dollahite et al. (1962)

Abbreviations: F = female; M = male; $NaNO_2$ = sodium nitrite; n.p. = not provided; s.c. = subcutaneous

Table 3. Short-Term and Subchronic Exposure to Pyrogallol (continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
rabbits (New Zealand, adult)	6 F, 6 M	hair dye formulation containing 0.4% pyrogallol	1 mL/kg of an equal (v/v) mixture of the hair dye with 6.0% hydrogen peroxide applied to the dorsolateral aspects of the shaven thoracic-lumbar area twice/week (areas were shampooed, rinsed, and dried 1 hour after application) Calculated pyrogallol dose = 2 mg/kg; 16 µmol/kg) twice/week	13-week exposure; sacrificed at the end of exposure period	No evidence of compound-induced toxicity was observed. The skin was thickened at the application sites, but this was expected by the authors due to the frequency of dye application. There were statistically significant differences in clinical chemistry and hematological values, although these were not considered to be toxicologically significant. No gross abnormalities or microscopic lesions were induced. Application sites were abraded once/week on half of the rabbits.	Burnett et al. (1976)
9.1.4.5 Cattle						
cattle (breed and age n.p.)	3 (sex n.p.)	pyrogallol, purity n.p.	400 mg/kg (3 mmol/kg) by gavage once per day	see Results/ Comments for exposure; observation period n.p.	1 animal experienced poisoning symptoms (n.p.) on day 2, which rapidly worsened, leading to death on day 4. The second animal developed poisoning symptoms like those of oak leaf poisoning on day 2. A third animal experienced poisoning symptoms on day 6.	Zhicheng (1992)

Abbreviations: F = female; M = male; $NaNO_2$ = sodium nitrite; n.p. = not provided; s.c. = subcutaneous

In the second study, guinea pigs were administered 0.1 mL of either a 100 or 500 mM solution (0.04 or 0.05 mmol pyrogallol) s.c. on three consecutive days into the feet, followed in the same week by another injection of the same dose near the neck (Masamoto and Takase, 1983; cited by CIR, 1991). As a challenge treatment four weeks later, either a fifth s.c. injection or a sealed-cloth application was administered. Both challenge treatments resulted in sensitization, which was dependent on the molar concentration of pyrogallol.

9.1.4.4 Rabbits

In a study designed to determine the repeated-dose oral LD_{50} for pyrogallol, rabbits were administered pyrogallol by gavage at 500 to 1000 mg/kg/day (4.0-7.93 mmol/kg/day) for ten days (Dollahite et al., 1962). The repeated-dose oral LD_{50} was 700 mg/kg/day (5.5 mmol/kg/day). Symptoms were similar to those found from acute dosing; in some animals, the lungs and liver were congested and the kidneys and spleen were congested and enlarged. Additionally, pyrogallol induced a smooth white exudate on the gastric mucosa and there were varying degrees of enteritis in the duodenum and cecum of some animals. The doses eliciting these responses were not provided.

In a 13-week study testing the toxicity of a hair dye formulation containing 0.4% pyrogallol, application of the formulation to the shaven and abraded skin of rabbits twice per week did not induce toxic symptoms or gross or microscopic anomalies (Burnett et al., 1976). The calculated pyrogallol dose was 2 mg/kg (16 μmol/kg) for each application.

9.1.4.5 Cattle

A 400 mg/kg/day (3.2 mmol/kg/day) oral dose of pyrogallol for up to 6 days induced symptoms of poisoning in 3 cattle; one of these animals subsequently died, and another exhibited symptoms similar to those of oak leaf poisoning (Zhicheng, 1992).

9.1.5 Chronic Exposure

The details of these studies are presented in **Table 4**.

9.1.5.1 Mice

Lifetime exposure to a 0.001, 0.005, or 0.01 mg (7.9, 40, or 79 nmol) pyrogallol in acetone applied to the skin of mice twice per week did not induce significant changes in the skin or shorten lifespan (Stenbäck and Shubik, 1974). Similarly, application of an oxidative hair dye containing 0.49% pyrogallol to the shaven skin of mice once per week for 9 or 20 months did not affect average body weight gain or survival; chronic inflammation of the skin was observed in both

Table 4. Chronic Exposure to Pyrogallol

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
9.1.5.1 Mice						
mice (Swiss, 7-wk-old)	50 F per dose	pyrogallol, purity n.p.	0.02 mL of 5, 25, or 50% pyrogallol (0.001, 0.005, or 0.01 mg; 7.9, 40, or 79 nmol) in acetone applied to the shaved dorsal skin between the flanks, twice per week	lifetime exposure (i.e., up to 27.5 months)	No significant changes in the skin were observed at any dose level. Hyperplasia, ulceration, or inflammation did not occur. 137/150 mice died by week 100 and all were dead by week 110.	Stenbäck and Shubik (1974)
mice (random-bred Swiss Webster, 8-wk-old)	60 F, 60 M per dose	oxidative hair dye formulation containing 0.49% pyrogallol	0.05 mL of an equal mixture of the hair dye and 6% H_2O_2 once per week to the shaven interscapular region calculated pyrogallol dose: 0.12 mg; 0.97 µmol)	20-month exposure for 50 F and 50 M; 9-month exposure for 10 F and 10 M; sacrificed at end of exposure period	Average body weight gain and survival were not adversely affected by treatment. Hematological and urinary values did not indicate toxicity. Chronic inflammation of the skin was observed in both treatment and control groups, but the authors stated that this finding was of little significance since the frequency and method of application results in substantial exaggerations of human exposure.	Jacobs et al. (1984)
9.1.5.2 Rabbits						
rabbits (New Zealand, 8-wk-old)	5 per dose (sex n.p.)	pyrogallol, purity n.p.	0.02 mL of 5, 25, or 50% pyrogallol (0.001, 0.005, or 0.01 mg; 7.9, 40, or 79 nmol) in acetone or methanol applied to the interior left ear, twice per week	lifetime exposure (i.e., up to 45 months)	All animals died before the 180th week of treatment. Treatment did not decrease survival rates or induce toxic responses at the application sites.	Stenbäck (1977)

Abbreviations: F = female; M = male; n.p. = not provided

treatment and control groups, and was not considered to be significant (Jacobs et al., 1984). The calculated pyrogallol dose was 0.12 mg twice/week (0.97 µmol twice/week).

9.1.5.2 Rabbits

As was observed with mice, lifetime dermal exposure to rabbits did not decrease survival rates or induce toxic responses at the application sites (Stenbäck, 1977). Pyrogallol was applied topically to the left ear twice per week for the life of the animals (i.e., ~ 180 weeks) at doses of 0.001, 0.005, or 0.01 mg (7.9, 40, or 79 nmol).

9.2 Reproductive and Teratogenic Effects

The details of these studies are presented in **Table 5**.

Pyrogallol induced few adverse reproductive effects in rats. A 300 mg/kg/day (2.38 mmol/kg/day) oral dose of pyrogallol to pregnant rats on days 6 to 15 of gestation induced a decrease in fetal body weights and an increase in the number of resorptions, whereas doses of 100 or 200 mg/kg/day (0.793 or 1.59 mmol/kg/day) induced no such effects (Picciano et al., 1982; 1983). Gross, visceral, or skeletal anomalies were not induced at any dose. In two dermal studies in which hair dye formulations containing 0.4% pyrogallol were applied to the skin of pregnant rats, no adverse effects were noted in maternal or fetal rats. In one study, the calculated pyrogallol dose was 8 mg/kg/day (63 µmol/kg/day) applied to the shaven skin of pregnant rats on days 1, 4, 7, 10, 13, 16, and 19 of gestation (Burnett et al., 1976). In the other study, by the International Research and Development Corporation (1977; cited by CIR, 1991), 1 mg (7.9 µmol) of pyrogallol was applied to rats twice per week throughout mating, gestation, and from lactation to weaning for 3 generations.

9.3 Carcinogenicity

The details of these studies are presented in **Table 6**.

9.3.1 Mice

Pyrogallol, when applied to the shaven skin of mice, was not carcinogenic in three dermal studies. In the first study, 0.02 mL of 5%, 25%, or 50% pyrogallol (0.001, 0.005, or 0.01 mg; 7.9, 40, or 79 nmol) was applied in acetone twice per week for the life of the animals (i.e., up to 110 weeks) (Stenbäck and Shubik, 1974), while in the second study, 5 mg (0.05 mmol) pyrogallol was applied three times per week for 440 days (Van Duuren and Goldshmidt, 1976). In the third study, 0.05 mL of an equal mixture of an oxidative hair dye formulation containing 0.49% pyrogallol and 6% H_2O_2 was applied once per week for 9 or 20 months; the calculated pyrogallol dose in the hair dye and H_2O_2 mixture was 0.12 mg/week (0.97 µmol/week) (Jacobs et al., 1984).

Table 5. Reproductive and Teratogenic Effects of Pyrogallol

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
rats (Sprague-Dawley, mature)	5 (lowest dose) or 6 (2 higher doses) F per group	pyrogallol, purity n.p.	100, 200, or 300 mg/kg/day (0.793, 1.59, or 2.38 mmol/kg) by gavage	exposed on days 6-15 of gestation; sacrificed on day 20 of gestation	Maternal lethality was not observed. Maternal rats receiving the high dose had significantly decreased mean body weight gain. The high dose induced a decrease in fetal body weights and an increased number of resorptions. No significant differences in gross, visceral, or skeletal anomalies were observed at any dose.	Picciano et al. (1982; 1983)
rats (Charles River CD, mature)	20 F	hair dye formulation containing 0.4% pyrogallol	2 mL/kg/day hair dye with an equal volume of H_2O_2 applied to shaved skin on the dorsoscapular area calculated pyrogallol dose: 8 mg/kg/day; 63 µmol/kg/day)	exposed on days 1, 4, 7, 10, 13, 16, and 19 of gestation; sacrificed on day 20 of gestation	Maternal toxicity was not observed. No significant differences in the number of corpora lutea, implantation sites, live fetuses, resorptions, or fetal soft tissue or skeletal anomalies were induced.	Burnett et al. (1976)
rats (Charles River CD, mature)	40 F, 40 M	hair dye formulation containing 0.4% pyrogallol	0.5 mL of an equal mixture (v/v) with 6% hydrogen peroxide applied to the skin twice/week calculated pyrogallol dose: 1 mg; 7.9 µmol) twice/week	exposed throughout mating, gestation, and from lactation to weaning for 3 generations	There were no treatment-related changes in general behavior and appearance, body weight, or survival in parents or offspring. Mild skin reactions were noted intermittently throughout the study. No effects on fertility, gestation, or viability were observed; gross or microscopic lesions were not induced.	International Research and Development Corporation (1977; cited by CIR, 1991)

Table 6. Carcinogenicity of Pyrogallol

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
9.3.1 Mice						
mice (Swiss, 7-wk-old)	50 F per dose	pyrogallol, purity n.p.	0.02 mL of 5, 25, or 50% pyrogallol (0.001, 0.005, or 0.01 mg; 7.9, 40, or 79 nmol) in acetone applied to the shaved dorsal skin between the flanks, twice per week	lifetime exposure (i.e., up to 27.5 months)	The number of neoplasms induced (i.e., lymphomas, pulmonary adenomas, and hepatic hemangiomas) was not statistically different from that of the control group. 137/150 mice died by week 100 and all were dead by week 110.	Stenbäck and Shubik (1974)

Abbreviations: BBN = *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine; DMSO = dimethyl sulfoxide; F = female; i.p. = intraperitoneal injection; M = male; n.p. = not provided; s.c. = subcutaneous

Table 6. Carcinogenicity of Pyrogallol (continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
mice (ICR/Ha Swiss, 6 to 8-wk-old)	50 F	pyrogallol, purity n.p.	5 mg (0.04 mmol) pyrogallol in acetone applied to the clipped dorsal skin 3 times per week	440-day exposure; sacrificed 2 months after clinical classification of tumors or when the animals became moribund	Treatment did not induce neoplasms.	Van Duuren and Goldschmidt (1976)
mice (random-bred Swiss Webster, 8-wk-old)	60 F, 60 M	oxidative hair dye formulation containing 0.49% pyrogallol	0.05 mL of an equal mixture of the hair dye and 6% H_2O_2 once per week to the shaven interscapular region calculated pyrogallol dose: 0.12 mg; 0.97 µmol)	20-month exposure for 50 F and 50 M; 9-month exposure for 10 F and 10 M; sacrificed at end of exposure period	The incidences of tumors (i.e., lung adenomas, liver hemanigomas, and malignant lymphomas) were not statistically different from those of the controls.	Jacobs et al. (1984)
9.3.2 Rats						
rats (F344, 6-wk-old)	15 M	pyrogallol, purity n.p.	0.5% in the diet	22-week exposure; sacrificed at the end of exposure	On day 22, the left ureter of all animals was ligated. Treatment did not significantly increase the incidences of papillar or nodular hyperplasia or papillomas of the urinary bladder.	Miyata et al. (1985)
rats (Fischer, 2-wk-old)	10 F, 9 M	pyrogallol purity n.p.	100 mg/kg/day (0.79 mmol/kg/day) s.c. in a 50% DMSO solution for 8 weeks followed by 14 mg/rat/day (0.11 mmol/rat) for 50 weeks	58-week exposure; observation period n.p.	3/9 M and 1/10 F rats had histiocytomas at the injection sites, while none of the control rats developed tumors.	Wang and Klemencic (1979)
9.3.3 Rabbits						

Abbreviations: BBN = *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine; DMSO = dimethyl sulfoxide; F = female; i.p. = intraperitoneal injection; M = male; n.p. = not provided; s.c. = subcutaneous

Table 6. Carcinogenicity of Pyrogallol (continued)

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
rabbits (New Zealand, 8-wk-old)	5 per dose (sex n.p.)	pyrogallol, purity n.p.	2 mL of 5, 25, or 50% pyrogallol solutions (0.001, 0.005, or 0.01 mg; 7.9, 40, or 79 nmol) in acetone or methanol applied to the interior left ear, twice per week	lifetime exposure (i.e., up to 45 months)	The only evidence of tumor formation was a uterine tumor in 1 rabbit treated with 50% pyrogallol.	Stenbäck (1977)

Abbreviations: BBN = *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine; DMSO = dimethyl sulfoxide; F = female; i.p. = intraperitoneal injection; M = male; n.p. = not provided; s.c. = subcutaneous

9.3.2 Rats

Feeding pyrogallol at 0.5% in the diet for 22 weeks did not induce hyperplasia or papillomas of the urinary bladder in rats (Miyata et al., 1985). However, injecting rats s.c. with 100 mg pyrogallol/kg/day (0.79 mmol/kg/day) for 8 weeks followed by 14 mg/rat/day (0.11 mmol/rat) for 50 weeks induced histiocytomas at the injection sites of 3/9 males and 1/10 females; none of the control rats developed tumors (Wang and Klemencic, 1979).

9.3.3 Rabbits

Lifetime exposure to 0.02 mL of a 50% pyrogallol solution (0.01 mg pyrogallol; 79 nmol) applied to the interior left ear twice per week induced a uterine tumor in 1 of 5 rabbits; 5% or 25% pyrogallol solutions (0.001 or 0.005 mg pyrogallol; 7.9 or 40 nmol) applied similarly induced no carcinogenic effects (Stenbäck, 1977).

9.4 Initiation/Promotion and Cocarcinogenicity

The details of these studies are presented in **Table 7**.

Pyrogallol acted as a potent cocarcinogen in one study, but was not a promoter in an initiation/promotion study. When 5 mg (0.04 mmol) pyrogallol and 0.005 mg B*a*P were simultaneously applied to the clipped dorsal skin of mice 3 times per week for 440 days, a significant number of squamous cell carcinomas (33/50) was observed; the authors characterized pyrogallol as a potent cocarcinogen (Van Duuren and Goldschmidt, 1976). In an initiation/promotion study, pyrogallol did not significantly promote hyperplasia or papillomas of the urinary bladder in rats given 0.05% BBN in the diet for two weeks followed by 0.5% pyrogallol in the diet for 22 weeks (Miyata et al., 1985).

9.5 Anticarcinogenicity

The details of this study are presented in **Table 8**.

BPL-induced neoplasia of the forestomach was not inhibited when pyrogallol (dose not provided) was administered by gavage to mice 4 hours prior to administration of 2 mg BPL by gavage twice per week for 12 weeks (Wattenberg et al., 1983).

9.6 Genotoxicity

The details of the these studies are presented in **Table 9**.

Table 7. Initiation/Promotion and Cocarcinogenicity Studies of Pyrogallol

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
mice (ICR/Ha Swiss, 6-8 wk-old)	50 F	pyrogallol and B*a*P, pure	5 mg (0.04 mmol) pyrogallol and 0.005 mg B*a*P (both in acetone) applied simultaneously to the clipped dorsal skin 3 times per week	440 day exposure; sacrificed 2 months after clinical classification of tumors or when the animals became moribund	12/50 of the control mice treated with only B*a*P developed squamous carcinomas, whereas 33/50 of the mice treated with BaP and pyrogallol developed tumors. The authors concluded that pyrogallol was a potent cocarcinogen since it nearly tripled the incidence of tumors induced by B*a*P alone.	Van Duuren and Goldschmidt (1976)
rats (F344, 6-wk-old)	14 M	pyrogallol and BBN, purities n.p.	0.05 % BBN (an initiator) in the diet for 2 weeks followed by 0.5% pyrogallol in the diet for 22 weeks	see dose for exposure period; sacrificed at the end of exposure	On day 22, the left ureter of all animals was ligated. Treatment did not significantly increase the incidences of papillar or nodular hyperplasia or papillomas of the urinary bladder.	Miyata et al. (1985)

Table 8. Anticarcinogenicity of Pyrogallol

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
mice (ICR/Ha, 9-wk-old)	20 F	pyrogallol, >97% pure, and BPL, purity n.p.	pyrogallol (dose n.p.) followed in 4 hours by 2 mg BPL, administered by gavage twice per week	12 week exposure; sacrificed at the end of exposure period	Pyrogallol did not significantly inhibit BPL-induced neoplasia of the forestomach. Neither the number of mice bearing forestomach tumors nor the number of tumors per mouse was reduced.	Wattenberg et al. (1983)

Abbreviations: B*a*P = benzo[*a*]pyrene; BBN = *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine; BPL = ß-propiolactone; F = female; M = male; n.p. = not provided

Table 9. Genotoxicity of Pyrogallol

Test System or Species, Strain, and Age	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
9.6.1 Acellular Systems							
DNA extracted from λ phage	DNA double strand breaks	n.p.	pyrogallol, purity n.p.	250 µM	positive	Reaction mixtures (i.e., DNA $CuSO_4$, pyrogallol, and sodium phosphate buffer [pH 6.7]) were incubated at 37°C for 6 hours.	Yamada et al. (1985)
pBR322 plasmid DNA	DNA double strand breaks in the presence and absence of Fe^{2+}	n.p.	pyrogallol, purity n.p.	1 mM	positive in the presence and absence of Fe^{2+}	The reaction mixture was incubated at 37°C for 30 min.	Lee et al. (1995)
calf thymus DNA	DNA damage in the presence and absence of Cu^{2+}	n.p.	pyrogallol, purity n.p.	0.18 mM	negative in the absence of Cu^{2+} positive in the presence of Cu^{2+}	DNA was incubated at 37°C for 1 hour with pyrogallol and $CuSO_4$ in sodium phosphate buffer under aerobic conditions	Hayakawa et al. (1997)
9.6.2 Prokaryotic Systems							
S. typhimurium strains TA98, TA100, and TA1537	*his* gene mutations	+/-	pyrogallol, purity n.p.	5-200 µg/plate (0.04-1.6 µmol/plate)	positive (TA100 and TA1537) negative (TA98)	The plate test was used. Ben-Gurion et al. (1979; 1981) stated that reduced mutagenicity in the presence of S9 was probably a result of an interaction with the mixture which reduced its activity toward the bacteria.	Ben-Gurion (1979; 1981)
S. typhimurium strains TA98, TA100, TA1535, and TA1537	*his* gene mutations	+/-	pyrogallol, purity n.p.	3.0 µmol/plate	positive (TA98 and TA100) negative (TA1535 and TA1537)	Spot test was used. A repeat test was conducted with TA98 and TA100 at 0.03-3.0 µmol/plate in the presence and absence of metabolic activation. In the test, a weakly positive response (TA98) and a negative response (TA100) were obtained. Florin et al. (1980) concluded that the mutagenicity to strains TA98 and TA100 was questionable.	Florin et al. (1980)

Abbreviations: F = female; i.p. = intraperitoneal; NA = not applicable; n.p. = not provided; p.o. = by mouth; SCE = sister chromatid exchange

Table 9. Genotoxicity of Pyrogallol

Test System or Species, Strain, and Age	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference

Table 9. Genotoxicity of Pyrogallol (continued)

Test System or Species, Strain, and Age	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
S. typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538	*his* gene mutations	+/-	pyrogallol, purity n.p.	up to 3600 µg/plate (28.5 µmol/plate)	positive (TA98 and TA100 with and without S9; TA1537 without S9) negative (TA1535 and TA1538 with and without S9; TA1537 with S9)	The plate incorporation assay was used.	Gocke et al. (1981)
S. typhimurium strain TA100	*his* gene mutations	+/-	pyrogallol, purity n.p.	100 µg/plate (0.79 µmol/plate)	positive	The plate incorporation assay was used. In the absence of S9, pyrogallol was moderately mutagenic. In the presence of S9, it was strongly mutagenic.	Yamaguchi (1981)
S. typhimurium strains TA98 and TA 1538	*his* gene mutations	+/-	pyrogallol, purity n.p.	20-1000 µg/plate (0.16-7.9 µmol/plate)	positive (TA98 without S9) negative (TA1538 with and without S9; TA98 with S9)	The plate incorporation assay was used. Pyrogallol was weakly mutagenic to TA98 without S9, but there was not a dose-response.	Picciano et al. (1983)
S. typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538	*his* gene mutations	+/-	pyrogallol, >98% pure (w/w)	50-5000 µg/plate (0.40-39.6 µmol/plate)	positive (TA100 and TA1537) negative (TA98, TA1535, and TA1538)	The plate incorporation assay was used.	Richold et al. (1984; cited by CIR, 1991)
			pyrogallol, 90-96% pure (w/w)	15-5000 µg/plate (0.12-39.6 µmol/plate)	positive (TA100 and TA1537) negative (TA98, TA1535, and TA1538)		

Abbreviations: F = female; i.p. = intraperitoneal; NA = not applicable; n.p. = not provided; p.o. = by mouth; SCE = sister chromatid exchange

Table 9. Genotoxicity of Pyrogallol (continued)

Test System or Species, Strain, and Age	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
S. typhimurium strains TA97, TA98, TA100, TA102, TA104, and TA1535	*his* gene mutations	-	pyrogallol, purity n.p.	6.25-200 µg/plate (0.0500-1.59 µmol/plate)	positive (TA97, TA100, TA102, TA104) negative (TA98, TA1535)	The plate incorporation assay was used. The positive results were obtained at the highest dose only. None of the doses tested were toxic to cells.	Glatt et al. (1989)
		+		1.25-500 µg/plate (0.00991-3.96 µmol/plate)	positive (TA97, TA100, TA104) negative (TA98, TA102, TA1535)	The positive results were obtained at the highest dose only. 400 µg/plate was toxic to cells.	
S. typhimurium strain REN	induction of colicin E2	-	pyrogallol, purity n.p.	5-600 µg/plate (0.040-4.8 µmol/plate)	positive	The colicin-induction plate test was used. Strain REN is a colicinogenic derivative of strain TA1537.	Ben-Gurion (1979)
S. typhimurium strain TA1535/pSK1002	induction of *umu* gene expression	+/-	pyrogallol, purity n.p.	100-3200 µg/mL (793-25,375 µM)	positive	The *umu* gene expression induced by pyrogallol at concentrations ≥ 2000 µg/mL (15,859 µM) was 6-fold the background level.	Sakagami et al. (1988)
9.6.3 *In Vitro* Lower Eukaryotic Systems							
Saccharomyces cerevisiae strain D7	mitotic gene conversion	n.p.	pyrogallol, purity n.p.	300 µg/mL (2380 µM)	positive at pH 10 negative at pH 7		Rosin (1984)
9.6.4 *In Vivo* Lower Eukaryotic Systems							
Drosophila melanogaster (Berlin K [wild type] and Basc, adult)	sex-linked recessive lethal mutations	NA	pyrogallol, purity n.p.	125 mM in feed	positive in the 1st of 3 broods tested	The dose tested was close to the LD_{50} value.	Gocke et al. (1981)
9.6.5 *In Vitro* Mammalian Systems							

Abbreviations: F = female; i.p. = intraperitoneal; NA = not applicable; n.p. = not provided; p.o. = by mouth; SCE = sister chromatid exchange

Table 9. Genotoxicity of Pyrogallol (continued)

Test System or Species, Strain, and Age	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
Chinese hamster ovary (CHO) cells	chromosomal aberrations and SCEs	+/-	pyrogallol, purity n.p.	100 µg/mL (793 µM)	positive		Stich et al. (1981)
	chromosome aberrations in the presence or absence of Cu^{2+} or Mn^{2+}	n.p.		10 µg/mL (79 µM)	negative (no metals or with Cu^{2+}) positive (with Mn^{2+})		
CHO K1 cells	chomosomal aberrations	n.p.	pyrogallol, purity n.p.	2.5, 5.0, or 10 µg/mL (20, 40, or 79 µM)	negative	10 µg/mL was toxic to cells.	Nakamura et al. (1997)
Chinese hamster V79 cells	induction of micronuclei	n.p.	pyrogallol, purity n.p.	up to 50 µM for 24 hours	positive	Higher concentrations were tested, but the frequency of micronucleated cells declined at concentrations above 50 µM; this phenomenon was attributed to the inhibition of cell proliferation.	Glatt et al. (1989)
Chinese hamster V79 cells	induction of SCEs	n.p.	pyrogallol, purity n.p.	up to 25 µM	positive	Pyrogallol was tested up to its toxic limit (varied with the endpoint).	Glatt et al. (1989)
L5178Y mouse lymphoma cells	mutagenicity	+/-	pyrogallol, purity n.p.	4.0-80.0 µg/mL (32-634 µM)	positive		Riach and McGregor (1984; cited by CIR, 1991)
human lymphocytes	chromosomal aberrations	-	pyrogallol, purity, n.p.	50, 75,or 100 µg/mL (400, 600, or 793 µM)	positive	Information on the mitogen used to stimulate the cells to proliferate and the exposure protocol was n.p.	Allen et al. (1984; cited by CIR, 1991)
		+		100, 500 or 1000 µg/mL (793, 3965, or 7930 µM)	positive		

Abbreviations: F = female; i.p. = intraperitoneal; NA = not applicable; n.p. = not provided; p.o. = by mouth; SCE = sister chromatid exchange

Table 9. Genotoxicity of Pyrogallol (continued)

Test System or Species, Strain, and Age	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
9.6.6 *In Vivo* Mammalian Systems							
mice (NMRI, age n.p.)	micronucleated polychromatic erythrocytes (MN-PCE)	NA	pyrogallol, purity n.p.	two i.p. doses of 252 mg/kg (2.0 mmol/kg) administered 24 hours apart	positive	Bone marrow was sampled 30 hours after treatment.	Gocke et al. (1981)
mice (strain n.p., 3 to 4-mo-old)	chromosomal aberrations	NA	pyrogallol, purity n.p.	single i.p. dose of 10, 20, or 30 mM	positive	The positive response was observed in bone marrow cells from mice treated with the 2 higher doses	Clairol (1981; cited by CIR, 1991)
mice (CBA x C57BL/6J)F_1, 60 to 75-day-old	MN-PCE	NA	pyrogallol purity n.p.	single i.p. dose of 75 mg/kg (0.59 mmol/ kg)	negative	Bone marrow was sampled 24, 48, 72, and 96 hours after treatment.	Paschin et al. (1986a)

Abbreviations: F = female; i.p. = intraperitoneal; NA = not applicable; n.p. = not provided; p.o. = by mouth; SCE = sister chromatid exchange

9.6.1 Acellular Systems

Pyrogallol, at 250 μM (32 μg/mL), induced double strand breaks in purified λ phage DNA (Yamada et al., 1985). At 1 mM (126 μg/mL), pyrogallol induced double strand breaks in pBR322 plasmid DNA, in the presence and absence of Fe^{2+} (Lee et al., 1995).

Pyrogallol, at 0.18 mM (23 μg/mL), induced DNA breakage in calf thymus DNA in the presence, but not in the absence, of Cu^{2+} (Hayakawa et al., 1997).

9.6.2 Prokaryotic Systems

A number of studies were conducted that investigated the ability of pyrogallol to induce *his* gene mutations in *Salmonella typhimurium* strains TA97, TA98, TA100, TA102, TA104, TA1535, TA1537, and TA1538.

In *S. typhimurium* strain TA97, pyrogallol was mutagenic in the presence and the absence of metabolic activation, when tested at concentrations of 3.96 μmol/plate (500 μg/plate) or 1.59 μmol/plate (200 μg/plate), respectively (Glatt et al., 1989).

Both positive and negative results were found when pyrogallol was tested for mutagenicity in *S. typhimurium* strain TA98. At concentrations ranging from 0.03 to 28.5 μmol/plate (4-3600 μg/plate), pyrogallol was found to be mutagenic in the presence of metabolic activation (Florin et al., 1980; Gocke et al., 1981) and in the absence of metabolic activation (Florin et al., 1980; Gocke et al., 1981; Picciano et al., 1983). In contrast, pyrogallolwas reported not to be mutagenic in strain TA98 in the presence of metabolic activation at concentrations ranging from 0.00991 to 39.6 μmol/plate (1.25-5000 μg/plate) (Ben-Gurion; 1979; Picciano et al., 1983; Glatt et al., 1984; Richold et al., 1984; cited by CIR, 1991) or, at concentrations ranging from 0.04 to 39.6 μmol/plate (5-5000 μg/plate), in the absence of metabolic activation (Ben-Gurion; 1979; 1981; Richold et al., 1984; cited by CIR, 1991; Glatt et al., 1989).

The majority of tests using *S. typhimurium* strain TA100 showed that pyrogallol was mutagenic at concentrations ranging from 0.4 to 39.6 μmol/plate (5-5000 μg/plate), both in the presence and the absence of metabolic activation (Ben-Gurion, 1979; 1981; Gocke et al., 1981; Yamaguchi; 1981; Richold et al., 1984; cited by CIR, 1991; Glatt et al., 1989). In contrast, Florin

et al (1980) reported that pyrogallol, at concentrations ranging from 0.03 to 3 µmol/plate (4-378 µg/plate), was not mutagenic in TA100 in a spot test, in the presence or absence of metabolic activation.

Pyrogallol, at 1.59 µmol/plate (200 µg/plate), was mutagenic in *S. typhimurium* strain TA102 in the absence of metabolic activation. In the presence of metabolic activation, no mutagenicity was seen in TA102 after exposure to 0.00991 to 3.96 µmol/plate (1.25-500 µg/plate) (Glatt et al., 1989).

Pyrogallol, at concentrations of 3.96 or 1.59 µmol/plate (500 or 200 µg/plate), was mutagenic in *S. typhimurium* strain TA104 in the presence and absence of metabolic activation, respectively (Glatt et al., 1989).

Pyrogallol was not mutagenic when tested in *S. typhimurium* strain TA1535 in the presence or absence of metabolic activation (Florin et al., 1980; Gocke et al., 1981; Richold et al., 1984; cited by CIR, 1991; Glatt et al., 1989). Pyrogallol was tested at concentrations ranging from 0.00991 to 39.6 µmol/plate (1.25-5000 µg/plate) in the presence of metabolic activation, and from 0.05 to 39.6 µmol/plate (6.25-5000 µg/plate) in the absence of metabolic activation.

Most tests showed that pyrogallol was mutagenic in *S. typhimurium* TA1537. Pyrogallol, at concentrations ranging from 0.12 to 39.6 µmol/plate (15-5000 µg/plate), was mutagenic in the presence (Ben-Gurion, 1979; Richold et al., 1984; cited by CIR, 1991) and absence (Ben-Gurion; 1979; 1981; Gocke et al., 1981; Richold et al., 1984; cited by CIR, 1991) of metabolic activation. In two tests, however, pyrogallol, at concentrations ranging between 3.0 and 28.5 µmol/plate (378-3600 µg/plate), was not mutagenic in the presence of metabolic activation (Florin et al., 1980; Gocke et al. 1981), and Florin et al. (1980) reported that pyrogallol, at 3 µmol/plate (378 µg/plate), was not mutagenic in the absence of metabolic activation.

Pyrogallol, at concentrations ranging from 0.12 to 39.6 µmol/plate (15-5000 µg/plate), was not mutagenic in *S. typhimurium* strain TA1538 in the presence or absence of metabolic activation (Gocke et al., 1981; Picciano et al., 1983; Richold et al., 1984; cited by CIR, 1991).

When pyrogallol, at concentrations of 0.040 to 4.8 µmol/plate (5-600 µg/plate), was

tested for its ability to induce colicin E2 in *S. typhimurium* strain REN, positive results were obtained (Ben-Gurion, 1979). Pyrogallol, at concentrations of 15,859 to 25,375 µM (100-3200 µg/mL), induced the expression of the *umu* gene in *S. typhimurium* strain TA1535/pSK1002; lower concentrations had no effect (Sakagami et al., 1988).

9.6.3 *In Vitro* Lower Eukaryotic Systems

Pyrogallol, at 2379 µM (300 µg/mL), when tested at pH 10 but not when tested at pH 7, induced gene conversion in *Saccharomyces cerevisiae* strain D7 (Rosin, 1984).

9.6.4 *In Vivo* Lower Eukaryotic Systems

When pyrogallol was administered orally at 125 mM (16 mg/mL) to *Drosophila melanogaster* strains Berlin K and Basc, sex-linked recessive lethal mutations were induced in the first of three broods (Gocke et al., 1981).

9.6.5 *In Vitro* Mammalian Systems

In CHO cells, pyrogallol at 793 µM (100 µg/mL) induced chromosomal aberrations and SCEs in the presence and absence of metabolic activation (Stich et al., 1981), but lower concentrations, ranging from 20 to 79 µM (2.5-10 µg/mL), had no such effect (Nakamura et al., 1997). At 79 µM (10 µg/mL), pyrogallol induced chromosome aberrations in CHO cells in the presence of Mn^{2+}, but not in the presence of Cu^{2+}; information on the presence or absence of metabolic activation was not provided (Stich et al., 1981).

In Chinese hamster V79 cells, pyrogallol, at concentrations up to 50 µM (6.3 µg/mL), induced micronuclei, and at concentrations up to 25 µM (3.2 µg/mL), it induced SCEs (Glatt et al., 1989).

At concentrations ranging from 32 to 634 µM (4-80 µg/mL), pyrogallol was mutagenic in L5178Y mouse lymphoma cells in the presence and absence of metabolic activation (Riach and McGregor, 1984; cited by CIR, 1991).

Pyrogallol induced chromosomal aberrations in human lymphocytes in the presence and absence of metabolic activation (Allen et al., 1984; cited by CIR, 1991). Pyrogallol was tested at concentrations ranging from 396 to 793 µM (50-100 µg/mL) in the absence of metabolic activation and at concentrations ranging from 793 to 7930 µM (100-1000 µg/mL) in the presence of metabolic activation. Information on the mitogen used to stimulate the cells to proliferate and the treatment protocol was not provided.

9.6.6 *In Vivo* Mammalian Systems

Pyrogallol increased the frequency of MN-PCE in mouse bone marrow when administered i.p. at 2 mmol/kg (252 mg/kg) (Gocke et al., 1981), but not at 0.59 mmol/kg (75 mg/kg) (Paschin et al., 1986a). Pyrogallol also induced chromosomal aberrations in mouse bone marrow cells when administered i.p. at 20 or 30 mM (2.5 or 3.8 mg/mL), but not when administered at 10 mM (1.3 mg/mL) (Clairol, 1981; cited by CIR, 1991).

9.7 Cogenotoxicity

The details of these studies are presented in **Table 10**.

When pBR322 plasmid DNA was incubated with 0.1 mM pyrogallol plus a nitric oxide-releasing compound (diethylamine compound with 1,1-diethyl-2-hydroxy-2-nitrosohydrazine, spermine compound with 1,1-diethyl-2-hydroxy-2-nitrosohydrazine, or sodium nitroprusside), DNA single strand breaks were induced (Yoshie and Ohshima, 1997). Treatment with pyrogallol or a nitric oxide-releasing compound alone did not induce a significant amount of breakage. In another test using pBR322 plasmid DNA, the strand breakage induced by nitric oxide-releasing compounds was prevented by excess superoxide dismutase; 1*H*-imidazol-1-yloxy,2-(4-

Table 10. Cogenotoxicity of Pyrogallol

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
pBR322 plasmid DNA	DNA single strand breaks	n.p.	pyrogallol, and NO-releasing compounds (DEA-NO, SPER-NO, and SNP), purity n.p.	0.1 mM pyrogallol plus 0.1 mM DEA-NO, SPER-NO, or SNP	positive	Incubated at 37°C for 1 hour. Pyrogallol and each of the NO-releasing compounds tested alone did not induce a significant amount of breakage. In another test, the strand breakage induced by NO-releasing compounds with pyrogallol was prevented by excess superoxide dismutase, carboxy-PTIO (an NO-trapping agent) or antioxidants (urate or ascorbate)	Yoshie and Ohshima (1997)
Saccharomyces cerevisiae strain MP1	enhancement of TEM-induced mutagenicity and recombinogenicity	n.p.	pyrogallol, ultra pure, and TEM, purity n.p.	up to 100 mM pyrogallol plus 24.5 µM TEM for 24 hours	positive	At low concentrations (n.p.), pyrogallol enhanced the mutagenic as well as the recombinogenic effect of TEM. At higher concentrations (n.p.), pyrogallol was comutagenic and antirecombinogenic.	Fahrig (1984)

Abbreviations: carboxy-PTIO = 1H-imidazol-1-yloxy, 2-(4-carboxyphenyl)-4,5-dihydro-4,4,5,5-tetramethyl-, 3-oxide, potassium salt; DEA-NO = diethylamine compound with 1,1-diethyl-2-hydroxy-2-nitrosohydrazine; NO = nitric oxide; n.p. = not provided; SNP = sodium nitroprusside; SPER-NO = spermine compound with 1,1-diethyl-2-hydroxy-2-nitrosohydrazine; TEM = triethylene melamine

carboxyphenyl-4,5-dihydro-4,4,5,5-tetramethyl-, 3-oxide, potassium salt (a nitric oxide-trapping agent); or antioxidants (urate or ascorbate) (Yoshi and Ohshima, 1997). When *S. cerevisiae* strain MP1 was treated with pyrogallol (at concentrations up to 100 mM) and triethylene melamine (TEM), Fahrig (1984) stated that the lower concentrations (not provided) of pyrogallol enhanced the mutagenic as well as the recombinogenic effect of TEM; at the higher concentrations (not provided), pyrogallol was comutagenic and antirecombinogenic.

9.8 Antigenotoxicity

The details of these studies are presented in **Table 11**.

9.8.1 Prokaryotic Systems

In two plate tests, pyrogallol inhibited B*a*P-induced mutagenicity in *S. typhimurium* strain TA98. In the first test, 100 µM (12.6 µg/mL) pyrogallol inhibited B*a*P-induced mutagenicity in the presence of S9, but not in the absence of S9 (Rahimtula et al., 1977). In the other test, pyrogallol, at 82 or 410 nmol/plate (10 or 52 µg/plate), inhibited B*a*P-induced mutagenicity when tested in the presence of metabolic activation; however inhibition at the high dose was simply due to toxicity (Calle and Sullivan, 1982). Based on an experiment in which pyrogallol inhibited rat liver microsomal mixed-function-oxidase-catalyzed hydroxylation of B*a*P *in vitro*, Rahimtula et al. (1977) concluded that pyrogallol inhibited this hydroxylation by a direct effect on cytochrome-P450.

9.8.2 Mammalian Systems *In Vitro*

Pyrogallol was tested for antigenotoxicity in three experiments using *in vitro* mammalian systems. In Chinese hamster V-70 [*sic*] somatic cells, pyrogallol, at concentrations up to 396 µM (50 µg/mL), inhibited B*a*P-induced mutagenicity (Pashin et al., 1986b). In C127 mouse mammary epithelial cells, pyrogallol (56 µM; 7.1 µg/mL) inhibited bovine papillomavirus-induced chromosome instability (Stich et al., 1990). In CHO cells, induction of chromosomal aberrations by mitomycin C was inhibited by pyrogallol at concentrations of 20 or 40 µM (2.5 or 5 µg/mL), but not at lower concentrations (Nakamura et al., 1997).

9.8.3 Mammalian Systems *In Vivo*

Pyrogallol, administered at 0.15 mmol/kg (18.8 mg/kg) i.p. to mice simultaneously with B*a*P, inhibited induction of MN-PCE by B*a*P in bone marrow (Paschin et al., 1986a). When pyrogallol (0.075 mmol/kg; 9.4 mg/kg) was administered concomitantly with dibunol (2,6-di-*tert*-butyl-4-methylphenol) and B*a*P, an even greater reduction in the number of MN-PCE induced by B*a*P was observed.

9.9 Immunotoxicity

The details of these studies are presented in **Table 12**.

Table 11. Antigenotoxicity of Pyrogallol

Test System or Species, Strain, and Age	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
9.8.1 Prokaryotic Systems							
Salmonella typhimurium strain TA98	inhibition of B*a*P-induced mutagenicity	+/-	pyrogallol and B*a*P, purity n.p.	100 µM pyrogallol plus 5 µg B*a*P/plate	positive in the presence of S9 and NADPH negative in the absence of S9	The plate test was used. The authors suggested that pyrogallol, as an antioxidant, exerts its protective effect against cancer by inhibiting the formation of carcinogenic metabolites.	Rahimtula et al. (1977)
S. typhimurium strain TA98	inhibition of B*a*P-induced mutagenicity	+	pyrogallol and B*a*P, purity n.p.	82 or 410 nmol pyrogallol/ plate plus 8.2 nmol B*a*P/plate	positive at both doses	The plate test was used. The positive response at the high dose was due to toxicity.	Calle and Sullivan (1982)
9.8.2 Mammalian Systems *In Vitro*							
Chinese hamster V70 somatic cells Please note: This study was translated from Russian and 'V70 somatic cells' may be a translation error.	inhibition of B*a*P-induced direct gene mutations at the HPRT locus	n.p.	pyrogallol and B*a*P, purity n.p.	up to 50 µg/mL (396 µM) pyrogallol, B*a*P concentration n.p.	positive for inhibition	A 1:1 B*a*P-pyrogallol ratio inhibited B*a*P-induced mutagenicity by 50%. A 1:2.5 ratio reduced induced mutations to a level close to the control value.	Pashin et al. (1986b)
C127 mouse mammary epithelial cells (strains BF3 and B5)	Inhibition of BPV-induced chromosome instability	NA	pyrogallol, purity n.p.	56 µM for 3 days	positive for inhibition	The BPV-transformed cells showed a persistently high incidence of mitotic irregularities detectable at anaphase and telophase, an elevated frequency of cells with micronuclei, and a broad spectrum of nuclear sizes. The response induced by pyrogallol was classified as a small inhibitory effect.	Stich et al. (1990)
Chinese hamster ovary K1 cells	inhibition of MMC-induced chromosomal	NA	pyrogallol and MMC, purity n.p.	0.625, 1.25, 2.5, or 5.0 µg pyrogallol/ mL (4.96, 9.91, 20,	positive for inhibition	The authors concluded that the inhibition was not due to cell cycle delay caused by	Nakamura et al. (1997)

Abbreviations: B*a*P = benzo[*a*]pyrene; BPV = bovine papillomavirus; dibunol = 2,6-di-*tert*-butyl-4-methylphenol; HPRT = hypoxanthine-guanine phosphoribosyl transferase; i.p. = intraperitoneal injection; MMC = mitomycin C; NA = not applicable; n.p. = not provided; PCE = polychromatic erythrocytes

Table 11. Antigenotoxicity of Pyrogallol

Test System or Species, Strain, and Age	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
	aberrations			or 40 µM) plus 0.85 µg/mL MMC		cytotoxicity.	

Table 11. Antigenotoxicity of Pyrogallol (continued)

Test System or Species, Strain, and Age	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
9.8.3 Mammalian Systems *In Vivo*							
mice (CBA x C57BL/6J)F_1, 60 to 75-day-old	inhibition of B*a*P-induced MN-PCE in bone marrow	NA	pyrogallol and B*a*P, purity n.p.	37.5 mg B*a*P plus 18.8 mg pyrogallol/kg (0.15 mmol/ kg), i.p.	positive for inhibition	Bone marrow was sampled 24, 48, 72, and 96 hours after a single treatment. At 48 hours after treatment (time of peak MN-PCE induction by B*a*P alone), pyrogallol reduced B*a*P-induced micronuclei formation by less than 50%.	Paschin et al. (1986a)
			pyrogallol, B*a*P, and dibunol, purity n.p.	37.5 mg B*a*P plus 9.4 mg pyrogallol/kg (0.075 mmol/ kg) and 9.4 mg dibunol/kg, i.p.		48 hours after treatment, there was an 80% reduction in B*a*P-induced MN-PCE.	

Table 12. Immunotoxicity of Pyrogallol

Test System or Species, Strain, and Age of Animal	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
rats (albino, adult)	pyrogallol and carrageenin,	25 mg/kg (0.20 mmol/kg)	Pyrogallol significantly inhibited carrageenin-induced edema.		Bhalla et al. (1970)

Abbreviations: B*a*P = benzo[*a*]pyrene; BPV = bovine papillomavirus; dibunol = 2,6-di-*tert*-butyl-4-methylphenol; HPRT = hypoxanthine-guanine phosphoribosyl transferase; i.p. = intraperitoneal injection; MMC = mitomycin C; NA = not applicable; n.p. = not provided; PCE = polychromatic erythrocytes

Table 12. Immunotoxicity of Pyrogallol

Test System or Species, Strain, and Age of Animal	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
	purity n.p.	pyrogallol i.p. 30 min. before carrageenin (0.05 mL of a 1% suspension) injection			
lymphocyte cultures from dissociated mouse splenic cells incubated with sheep red blood cells for 4-5 days	pyrogallol, purity n.p.	5 µg/culture (0.04 µmol/culture)	Treatment suppressed plaque formation by >90%.	The Mishell-Dutton system was used. The author stated that the immunosuppressive effect was not due to overt toxicity.	Archer (1978)

Abbreviations: B*a*P = benzo[*a*]pyrene; BPV = bovine papillomavirus; dibunol = 2,6-di-*tert*-butyl-4-methylphenol; HPRT = hypoxanthine-guanine phosphoribosyl transferase; i.p. = intraperitoneal injection; MMC = mitomycin C; NA = not applicable; n.p. = not provided; PCE = polychromatic erythrocytes

Pyrogallol, when administrated i.p. to rats at 0.20 mmol/kg (25 mg/kg), significantly inhibited carrageenin-induced edema (Bhalla et al., 1970). At 0.04 µmol/culture (5 µg/culture), pyrogallol exhibited an immunosuppressive effect by suppressing plaque (zone of lysis) formation in lymphocyte cultures from dissociated mouse splenic cells incubated with sheep red blood cells (Archer, 1978).

9.10 Anti-Immunotoxicity

The details of this study are presented in **Table 13**.

When mice were treated topically with solutions containing pyrogallol at concentrations up to 20%, significant reductions of Langerhans cell ATPase (a target of all forms of dermatological therapy) were observed with ointments containing ≥5% pyrogallol (other contents of the ointments not provided) (Gruner et al., 1992). No inhibition of 1-fluoro-2,4-dinitrobenzene-induced contact hypersensitivity was seen at any of the tested pyrogallol concentrations.

9.11 Other Data

9.11.1 Inhibition of the Nitrosation Reaction *In Vitro*

Pyrogallol suppressed the formation of mutagenic nitrosation products of secondary amines and amides *in vitro* (Yamada et al., 1978; Stich et al., 1982). The secondary chemicals used include dimethylamine, diethylamine, pyrrolidine, and piperidine (Nakamura and Kawabata, 1981), and methylurea (Yamamoto et al., 1988). Since many *N*-nitrosamines (IARC, 1978) and *N*-nitrosamides (Magee and Barnes, 1967; Montesano and Bartsch, 1976; both cited by Yamamoto et al., 1988) are direct mutagens and potent carcinogens in target organs of animals, their formation in the environment or in the human body is an important consideration in the study of carcinogenesis (Yamamoto et al., 1988).

9.11.2 Protooncogene Expression

Pyrogallol (200 µM; 25 µg/mL) induced c-*fos* and c-*jun* protooncogene expression in quiescent human hepatoma HepG2 cells (Choi and Moore, 1993).

9.11.3 Enzyme Effects

It is well documented that pyrogallol inhibits COMT activity (Booth et al., 1959; Archer et al., 1960; Daly et al., 1960; all cited by Guldberg and Marsden, 1975; Crout et al., 1961; Ross and Haljasmaa, 1964; both cited by Rogers et al., 1968; Glavas et al., 1967; Angel and Rogers, 1968; Baldessarini and Greiner, 1973; Caillard et al., 1973; Rubenstein et al., 1975; Latour and Léger-Gauthier, 1978; Petersen and Hjelle, 1982; Smit et al., 1994). Pyrogallol not only competitively inhibits COMT, but also acts as a substrate for the enzyme (Axelrod, 1966; cited by Glavas et al., 1967). As a COMT inhibitor, pyrogallol prolongs the action of epinephrine and the response to sympathetic nerve stimulation (Bacq et al., 1959; cited by Glavas et al., 1967).

Table 13. Anti-Immunotoxicity of Pyrogallol

Species, Strain, and Age	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
mice (Balb/c, age n.p.)	pyrogallol, purity n.p.	up to 20% pyrogallol applied topically	Pyrogallol concentrations ≥ 5% significantly reduced Langerhans cell ATPase. Treatment did not inhibit DNFB-induced contact hypersensitivity	Langerhans cell ATPase is a target of all forms of dermatological therapy.	Gruner et al. (1992)

Abbreviations: DNFB = 1-fluoro-2,4-dinitrobenzene; i.p. = intraperitoneal injection; n.p. = not provided

Pyrogallol has also been found to inhibit the activities of rat liver aldehyde dehyrogenase (Rubenstein et al., 1975), human melanoma tyrosinase (Chen and Chavin, 1978), ribonucleotide reductase in intact Ehrlich ascites tumor cells (Liermann et al., 1990), hog thyroid peroxidase (Cooksey et al., 1985), and human splenic protein tyrosine kinase (Lázaro et al., 1995).

Pyrogallol exhibited co-oxidase activity when tested *in vitro* with human liver lipoxygenase (Roy and Kulkarni, 1996).

10.0 STRUCTURE-ACTIVITY RELATIONSHIPS

Based on a relatively small study of the clastogenic activity of substituted phenols, monohydroxylated phenols (e.g., *p*-hydroxybenzoic acid, salicylic acid, and *p*-coumaric acid) seem to lack clastogenic activity, whereas dihydroxylated phenolics (e.g., catechol, 4-methyl catechol, resorcinol, protocatechuic acid, and caffeic acid) and trihydroxylated phenolics (phloroglucinol, pyrogallol, and gallic acid) exhibit relatively strong chromosome-damaging potential (Stich et al., 1981). The introduction of an *O*-methyl group seemed to reduce the clastogenic capability of hydroxylated phenols.

The inhibition of B*a*P-induced mutagenicity by polyhydric phenols is related to the presence of reactive hydrogen atoms that inhibit free-radical self-oxidation reactions of the chemical mutagen (Pashin et al., 1986b). The number of reactive hydrogen atoms in a series of polyhydric phenols (i.e., phenol, resorcinol, and pyrogallol) increased with an increase in the number of hydroxyl groups and was responsible for the antimutagenic properties of these simple polyhydric phenols.

In a study of naturally occurring compounds found in plants, those that contained a pyrogallol moiety (i.e., gallic acid, (-)-epicatechin gallate, (-)-epigallocatechin, and (-)-epigallocatechin gallate) inhibited UV-induced mutations in *E. coli*, while compounds without the pyrogallol moiety (i.e., caffeic acid, chlorogenic acid, and quercetin) had no such effect (Shimoi et al., 1986). The authors stated that the compounds with a pyrogallol moiety may stimulate the removal of photo products, but the mechanism of action was not determined.

11.0 ONLINE DATABASES AND SECONDARY REFERENCES

11.1 Online Databases

Chemical Information System Files

SANSS
TSCATS (Toxic Substances Control Act Test Submissions)

DIALOG Files

Kirk-Othmer Encyclopedia of Chemical Technology

National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files

AGRICOLA	CHEMLIST	MEDLINE
BIOSIS	EMBASE	Registry
CANCERLIT	HSDB	RTECS
CAPLUS	LIFESCI	TOXLINE

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSHTIC7	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA

Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

Databases Available on the Internet

Phytochemeco Database (Agricultural Research Service)

In-House Databases

Current Contents on Diskette ®
The Merck Index, 1996, on CD-ROM

11.2 Secondary References

The Merck Index, 12th ed., Budavari, S. Ed. Merck & Co., Inc., Whitehall, NJ. Listed in Section 12 as Budavari (1996).

12.0 REFERENCES

21 CFR 73.1375. Pyrogallol. Listing of color additives exempt from certification.

21 CFR 73.1025. Ferric ammonium citrate.

21 CFR 101.108. Temporary exemptions for purposes of conducting authorized food labeling experiments.

Aeschbacher, H.-U. 1991. Chapter 9: Mutagenic and Antimutagenic Compounds in Beverages. In: H. Hayatsu (Ed.), Mutagens in Food: Detection and Prevention. CRC Press, Inc., Boca Raton, FL. pp. 181-191.

Allen, J. A., P. C. Brooker, D. M. Birt, and K. J. McCaffrey. 1984. Submission of unpublished data to the Environmental Protection Agency. Technical synthetic pyrogallol: Metaphase chromosome analysis of human lymphocytes cultured in vitro. Chesterford Park Research Station. Saffron Walden, Essex, England. (Cited by CIR, 1991)

Angel, A., and K. J. Rogers. 1968. Convulsant action of polyphenols. Nature 217(5123):84-85.

Angel, A., and. K. J. Rogers. 1972. An analysis of the convulsant activity of substituted benzenes in the mouse. Toxicol. Appl. Pharmacol. 21:214-229.

Angel, A., R. N. Lemon, K. J. Rogers, and P. Banks. 1969. The effect of polyhydroxyphenols on brain ATP in the mouse. Exp. Brain Res. 7:250-257. (Cited by CIR, 1991)

Angelini, G., G. A. Vena, G. Giglio, F. Fiordalisi, and C. L. Meneghini. 1985. Epidemiology of contact dermatitis. Trans. St. John's Hosp. Dermatol. Soc. 55:17. (Cited by CIR, 1991)

Archer, D. L. 1978. Immunotoxicology of foodborne substances: An overview. J. Food Prot. 41(12):983-988.

Archer, S., A. Arnold, R. K. Kullnig, and D. W. Wylie. 1960. The enzymic methylation of pyrogallol. Arch. Biochem. Biophys. 87:153-54. (Cited by Guldberg and Marsden, 1975)

Axelrod, J. 1966. Methylation reactions in the formation and metabolism of catecholamines and other biogenic amines. Pharmacol. Rev. 18:95. (Cited by Glavas et al., 1967)

Azhar, N. G., and D. C. Stuckey. 1994. The influence of chemical structure on the anaerobic catabolism of refractory compounds: A case study of instant coffee wastes. Water Sci. Technol. 30(12):223-232.

Bacq, Z. M., L. Gosselin, A. Dresse, and J. Renson. 1959. Inhibition of *O*-methyltransferase by catechol and sensitization to epinephrine. Science 130:453. (Cited by Glavas et al., 1967)

Bakke, O. M. 1970. *O*-Methylation of simple phenols in the rat. Acta Pharmacol. Toxicol. 28:28-38.

Baldessarini, R. J., and E. Greiner. 1973. Inhibition of catechol-*O*-methyltransferase by catechols and polyphenols. Biochem. Pharmacol. 22:247-256.

Ben-Gurion, R. 1979. Mutagenic and colicine [*sic*]-inducing activity of two antioxidants: Pyrogallol and purpurogallin. Mutat. Res. 68:201-205.

Bhalla, T. N., J. N. Sinha, K. K. Tangri, and K. P. Bhargava. 1970. Role of catecholamines in inflammation. Eur. J. Pharmacol. 13:90-96.

Booth, A. N., M. Masri, D. J. Robbins, O. H. Emerson, F. T. Jones, and F. Deeds. 1959. The metabolic fate of gallic acid and related compounds. J. Biol. Chem. 234:3014-3016. (Cited by Guldberg and Marsden, 1975)

Budavari, S. Ed. 1996. Pyrogallol. In: The Merck Index. 12th ed., Merck & Co., Inc., Whitehall, NJ. pp. 1375-1376.

Burnett, C., E. I. Goldenthal, S. B. Harris, F. X. Wazeteer, J. Strausburg, R. Kapp, and R. Voelker. 1976. Teratology and percutaneous toxicity studies on hair dyes. J. Toxicol. Environ. Health 1(6):1027-1040.

Caillard, C., J. R. Rapin, J. Bralet, and P. Rossignol. 1973. *Modification par la désipramine chez le rat de la sensibilisation adrénergique du pyrogallol*. Arch. Int. Pharmacodyn. 202:153-162. Abstract in English.

Calle, L. M., and P. D. Sullivan. 1982. Screening of antioxidants and other compounds for antimutagenic properties towards benzo[*a*]pyrene-induced mutagenicity in strain TA98 of *Salmonella typhimurium*. Mutat. Res. 101:99-114.

Chen, Y. M., and W. Chavin. 1978. *In vitro* effects of melanocytolytic agents and other compounds upon dominant human melanoma tyronisinase activity. Experientia 34(1):21-22.

Choi, H.-S., and D. D. Moore. 1993. Induction of c-*fos* and c-*jun* gene expression by phenolic antioxidants. Mol. Endocrinol. 7(12):1596-1602.

CIR (Cosmetic Ingredient Review Expert Panel). 1991. Final Report on the Safety Assessment of Pyrogallol. J. Am. Coll. Toxicol. 10(1):67-85.

Clairol. 1979a. Submission of unpublished data by CTFA. Rabbit eye irritation study. (Cited by CIR, 1991)

Clairol. 1979b. Submission of unpublished data by CTFA. Studies in guinea pigs to determine the potential of hair dyes to induce allergic contact dermatitis. (Cited by CIR, 1991)

Clairol. 1981. Submission of unpublished data by CTFA. Oral LD_{50} in male rats. (Cited by CIR, 1991)

Clayton, G. D., and F. E. Clayton. 1981. Patty's Industrial Hygiene and Toxicology, 3rd ed., rev. Vol. IIA, John Wiley and Sons, New York. p. 2594. (Cited by CIR, 1991, and HSDB, 1996)

Collins, M. A., R. Gordon, Jr., M. G. Bigdeli, and J. A. Rubenstein. 1974. Pyrogallol potentiates acetaldehyde blood levels during ethanol oxidation in rats. Chem.-Biol. Interactions 8:127-130.

Cooksey, R. C., E. Gaitan, R. H. Lindsay, J. B. Hill, and K. Kelly. 1985. Humic substances, a possible source of environmental goitrogens. Org. Geochem. 8(1):77-80.

Crout, J. R., C. R. Creveling, and S. Udenfriend. 1961. Norepinephrine metabolism in rat brain and heart. J. Pharmacol. Exp. Ther. 132:269-277. (Cited by Rogers et al., 1968, and Guldberg and Marsden, 1975)

CTFA (Cosmetic, Toiletry, and Fragrance Association). [year not provided]. Submission of unpublished data by CTFA. Cosmetic ingredient chemical description of pyrogallol. (Cited by CIR, 1991)

Daly, J. W., J. Axelrod, and B. Witkop. 1960. Dynamic aspects of enzymatic *O*-methylation and -demethylation of catechols *in vitro* and *in vivo*. J. Biol. Chem. 235:1155-1159. (Cited by Guldberg and Marsden, 1975)

Dollahite, J. W., R. F. Pigeon, and B. J. Camp. 1962. The toxicity of gallic acid, pyrogallol, tannic acid, and *Quercus havardi* in the rabbit. Am. J. Vet. Res. 23(97):1264-1267.

Dorland's Illustrated Medical Dictionary. 1994. 28th ed. W. B. Saunders Co., Philadelphia.

Eccleston, D., and I. M. Ritchie. 1973. Sulphate ester formation from catechol amine metabolites and pyrogallol in rat brain *in vivo*. J. Neurochem. 21(3):635-646.

Fahrig, R. 1984. Genetic mode of action of cocarcinogens and tumor promoters in yeast and mice. Mol. Gen. Genet. 194:7-14.

FDA (Food and Drug Administration). 1989. Cosmetic product formulation data. FDA computer printout. (Cited by CIR, 1991)

Florin, I., L. Rutberg, M. Curvall, and C. R. Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 15:219-232.

Frosch, P. J., D. Burrows, J. G. Camarasa, A. Dooms-Goossens, G. Ducombs, A. Lahti, T. Menné, R. J. G. Rycroft, S. Shaw, I. R. White, and J. D. Wilkinson. 1993. Allergic reactions to a hairdressers' series: Results from 9 European centres. Contact Dermatitis 28:180-183.

Gardella, J. L., J. A. Izquierdo, and I. Izquierdo. 1970. The analgesic action of catecholamines and of pyrogallol. Eur. J. Pharmacol. 10(1):87-90.

Glatt, H., R. Padykula, G. A. Berchtold, G. Ludewig, K. L. Platt, J. Klein, and F. Oesch. 1989. Multiple activation pathways of benzene leading to products with varying genotoxic characteristics. Environ. Health Perspect. 82:81-89.

Glavas, E., T. Trajkov, and B. Nikodijevic. 1967. Cardiovascular effects of pyrogallol and 4-tropoloneacetamide. Arch. Int. Pharmacodyn. 170(1):134-137.

Gocke, E., M.-T. King, K. Eckhardt, and D. Wild. 1981. Mutagenicity of cosmetics ingredients licensed by the European Communities. Mutat. Res. 90:91-109.

Gosselin, R. E., et al. [other editors not provided], Eds. 1981. Clinical Toxicology of Commercial Products, 5th ed. Wilkins & Wilkins, Baltimore. p. 190.

Grayson, M. Ed. 1985. Pyrogallol. In: Kirk-Othmer Concise Encyclopedia of Chemical Technology. John Wiley & Sons, New York. p. 931.

Gruner, S., A. Zwirner, D. Strunk, and N. Sönnichsen. 1992. The influence of topical dermatological treatment modalities on epidermal Langerhans cells and contact sensitization in mice. Contact Dermatitis 26:241-247.

Guerra, L., A. Tosti, F. Bardazzi, P. Pigatto, P. Lisi, B. Santucci, R. Valsecchi, D. Schena, G. Angelini, A. Sertoli, F. Ayala, and F. Kokelj. 1992a. Contact dermatitis in hairdressers: The Italian experience. Contact Dermatitis 26:101-107.

Guerra, L., F. Bardazzi, and A. Tosti. 1992b. Contact dermatitis in hairdressers' clients. Contact Dermatitis 26:108-111.

Guldberg, H. C., and C. A. Marsden. 1975. Catechol-*O*-methyltransferase: Pharmacological aspects and physiological role. Pharmacol. Rev. 27(2):135-206.

Hayakawa, F., T. Kimura, T. Maeda, M. Fujita, H. Sohmiya, M. Fujii, and T. Ando. 1997. DNA cleavage reaction and linoleic acid peroxidation induced by tea catechins in the presence of cupric ion. Biochim. Biophys. Acta 1336:123-131.

Hirose, M., T. Inoue, M. Asamoto, Y. Tagawa, and N. Ito. 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(8):1285-1289.

HSDB (Hazardous Substances Databank). 1996. Pyrogallol. HSDB No. 794. Profile updated on Jan. 19, 1996.

IARC(International Agency for Research on Cancer). 1978. General remarks on the substances considered. IARC Monogr. Eval. Carcinog. Risks Humans. Vol. 17(Some *N*-Nitroso Compounds):35-47.

International Research and Development Corporation. 1977. Submission of unpublished data by CTFA. Multigeneration study in rats. (Cited by CIR, 1991)

Izquierdo, J. A., I. J. Jofre, and M. A. Dezza. 1964. Effect of pyrogallol on the catecholamine contents of the cortex, diencephalon, mesencephalon, rhombencephalon and cerebellum of mouse and rat. Medna Exp. 10:45-55. (Cited by Guldberg and Marsden, 1975)

Jacobs, M. M., C. M. Burnett, A. J. Penicnak, J. A. Herrera, W. E. Morris, P. Shubik, M. Apaja, and G. Granroth. 1984. Evaluation of the toxicity and carcinogenicity of hair dyes in mice. Drug Chem. Toxicol. 7(6):573-586.

Jahnig, C. E., and R. R. Bertrand. 1976. Aqueous effluents from coal-conversion processes. Chem. Eng. Prog. 72:51. (Cited by Cooksey et al, 1985)

Keil, H. 1962. Group reactions in contact dermatitis due to resorcinol. Arch. Dermatol. 86:212-216.

Klibanov, A. M., T. M. Tu, and K. P. Scott. 1983. Peroxidase-catalyzed removal of phenols from coal-conversion wastewaters. Science 221: 259-261. (Cited by Cooksey et al., 1985)

Kokelj, F., and A. Cantarutti. 1986. Contact dermatitis in leg ulcers. Contact Dermatitis 15(1):47-49.

Latour, J.-G., and C. Léger-Gauthier. 1978. Sensitization to the generalized Shwartzman reaction by catechol-*O*-methyltransferase inhibitors. Am. J. Pathol. 92(2):377-387.

Lázaro, I., C. Palacios, M. González, and P. González-Porqué. 1995. Inhibition of human spleen protein tyrosine kinases by phenolic compounds. Anal. Biochem. 225(1):180-183.

Lee, S. F., Y. C. Liang, and J. K. Lin. 1995. Inhibition of 1,2,4-benzenetriol-generated active oxygen species and induction of phase II enzymes by green tea polyphenols. Chem.-Biol. Interactions 98:283-301.

Liermann, B., G. Lassmann, and P. Langen. 1990. Quenching of tyrosine radicals of M2 subunit from ribonucleotide reductase in tumor cells by different antitumor agents: An EPR study. Free Radical Biol. Med. 9:1-4.

Malkinson, A. M. 1979. Prevention of butylated hydroxytoluene-induced lung damage in mice by cedar terpene administration. Toxicol. Appl. Pharmacol. 49:551-560.

Magee, P. N., and J. M. Barnes. 1967. Carcinogenic nitroso compounds. Adv. Cancer Res. 10:163-246. (Cited by Yamamoto et al., 1988)

Maitre, L. 1966. Effects of long-term administration of pyrogallol on tissue catecholamine levels, monoamine oxidase, and catechol-*O*-methyltransferase activities in the rat. Biochem. Pharmacol. 15:1935-1945. (Cited by Guldberg and Marsden, 1975)

Masamoto, Y., and Y. Takase. 1983. Action of phenols on the skin. II. Delayed contact sensitivity and bovine serum albumin binding of mono-, di-, and trivalent phenols. Shinshu. Igaku, Zasshi. 31(6):522-528. (Cited by CIR, 1991)

Matsouka, M., H. Yoshida, and R. Imaizumi. 1962. Effect of pyrogallol on the catecholamine content of rabbit brain. Biochem. Pharmacol. 11:1109-1110. (Cited by Guldberg and Marsden, 1975)

McCann, M. F. 1992. Occupational and environmental hazards in art. Environ. Res. 59:139-144.

Meffert, H. 1970. Acceleration of UV-induced lipid peroxidation by anti-psoriatics. Derm. Monnatsschr. 156:489. (Cited by Willsteed and Regan, 1985)

Miller, B. A., and A. Blair. 1983. Mortality patterns among press photographers. J. Occup. Med. 25(6):439-442.

Miyata, Y., S. Fukushima, M. Hirose, T. Masui, and N. Ito. 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. 76:828-834.

Montesano, R., and H. Bartsch. 1976. Mutagenic and carcinogenic N-nitroso compounds: Possible environmental hazards. Mutat. Res. 32:179-228. (Cited by Yamamoto et al., 1988)

Nakamura, M., and T. Kawabata. 1981. Effect of Japanese green tea on nitrosamine formation *in vitro*. J. Food Sci. 46:306-307.

Nakamura, T., Y. Nakazawa, S. Onizuka, S. Satoh, A. Chiba, K. Sekihashi, A. Miura, N. Yasugahira, and Y. F. Sasaki. 1997. Antimutagenicity of Tochu tea (an aqueous extract of *Eucommia ulmoides* leaves): 1. The clastogen-suppressing effects of Tochu tea in CHO cells and mice. Mutat. Res. 388:7-20.

Nor-Am Chemical Company. 1985. Letter to the Environmental Protection Agency. Occupational exposure to pyrogallol. (Cited by CIR, 1991)

Ohshima, H., M. Friesen, C. Malaveille, I. Brouet, A. Hautefeuille, and H. Bartsch. 1989. Formation of direct-acting genotoxic substances in nitrosated smoked fish and meat products: Identification of simple phenolic precursors and phenyldiazonium ions as reactive products.

Paschin, Y. V., L. M. Bakhitova, and T. I. Benthen. 1986a. Increased antimutagenic activity of simple substituted phenols mixed with hindered phenolic antioxidant dibunol. Food Chem. Toxicol. 24(8):881-883.

Pashin Y. V., L. M. Bakhitova, and T. I. Bentkhen [different transliteration of names from that shown above]. 1986b. Dependence of antimutagenic activity of simple phenols on the number of hydroxyl groups. Bull. Exp. Biol. Med. (USSR) 102:1121-1123.

Petersen, D. R., and J. J. Hjelle. 1982. Metabolic interactions of aldehyde dehydrogenase with therapeutic and toxic agents. Prog. Clin. Biol. Res. 114:103-120.

Pettersson, B., M. Curvall, and C. R. Enzell. 1982. Effects of tobacco smoke compounds on the ciliary activity of the embryo chicken trachea *in vitro*. Toxicology 23:41-55.

Picciano, J. C., W. E. Morris, and B. A. Wolf. 1982. The absence of teratogenic effects of several oxidative dyes in Sprague-Dawley rats. J. Am. Coll. Toxicol. 1(3):155.

Picciano, J. C., W. E. Morris, S. Kwan, and B. A. Wolf. 1983. Evaluation of the teratogenic and mutagenic potential of the oxidative dyes, 4-chlororesorcinol, *m*-phenylenediamine, and pyrogallol. J. Am. Coll. Toxicol. 2(4):325-333.

Pitt, W. W., R. L. Jolley, and G. Jones. 1979. Characterization of organics in aqueous effluents of coal-conversion plants. Environ. Int. 2:167-171. (Cited by Cooksey et al., 1985)

Pweny, R. 1925. A case of toxicity of pyrogallic acid. J. Am. Med. Assoc. 85:555. (Cited by Willsteed and Regan, 1985)

Rahimtula, A. D., P. K. Zachariah, and P. J. O'Brien. 1977. The effects of antioxidants on the metabolism and mutagenicity of benzo[*a*]pyrene *in vitro*. Biochem. J. 164:473-475.

Riach, C. G., and D. B. McGregor. 1984. Submission of unpublished data to the Environmental Protection Agency. Technical synthetic pyrogallol. Mouse lymphoma mutation assay. Chesterford Park Research Station. Saffron Walden, Essex, England. (Cited by CIR, 1991)

Richold, M., E. Jones, and L. A. Fenner. 1984. Submission of unpublished data to the Environmental Protection Agency. Technical synthetic and technical natural pyrogallol. Ames bacterial mutagenicity test. Chesterford Park Research Station. Saffron Walden, Essex, England. (Cited by CIR, 1991)

Rodnan, N. 1997. Pyrogallol. In: Chemcyclopedia 98. American Chemical Society, Washington, D.C. p. 184.

Rogers, K. J., A. Angel, and L. Butterfield. 1968. The penetration of catechol and pyrogallol into the mouse brain and the effect on cerebral monoamine levels. J. Pharm. Pharmacol. 20:727-729.

Rosin, M. P. 1984. The influence of pH on the convertigenic activity of plant phenolics. Mutat. Res. 135:10-113.

Ross, S. B., and Ö. Haljasmaa. 1964. Catechol-*O*-methyl transferase inhibitors. *In vivo* inhibition in mice. Acta Pharmacol. Toxicol. 21:215-225. (Cited by Rogers et al., 1968)

Rossi, A. M., and P. R. Burgmayer. 1991. Hydroxyalkylhydroxylamine as oxygen scavengers for use in aqueous media. U.S. patent no. 91-675376 910326. Abstract in CAPLUS 1993:66547.

Roy, S. K., and A. P. Kulkarni. 1996. Isolation and some properties of dioxygenase and co-oxidase activities of adult human liver cytosolic lipoxygenase. J. Biochem. Toxicol. 11(4):161-174.

Rubenstein, J. A., M. A. Collins, and B. Tabakoff. 1975. Inhibition of liver aldehyde dehydrogenase by pyrogallol and related compounds. Experientia 31(4):414-415.

Sakagami, Y., H. Yamazaki, N. Ogasawara, H. Yokoyama, Y. Ose, and T. Sato. 1988. The evaluation of genotoxic activities of disinfectants and their metabolites. Mutat. Res. 209:155-160.

Sax, I. N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Company, New York. p. 949. (Cited by CIR, 1991)

Schafer, Jr., E. W., W. A. Bowles, Jr., and J. Hurlbut. 1983. The acute oral toxicity, repellency, and hazard potential of 998 chemicals to one or more species of wild and domestic birds. Arch. Environ. Contam. Toxicol. 12:355-382.

Scheline, R. R. 1966. The decarboxylation of some phenolic acids by the rat. Acta Pharmacol. Toxicol. 24(2-3):275-285. (Cited by CIR, 1991)

Scheline, R. R. 1968. The metabolism of drugs and other organic compounds by the intestinal microflora. Acta Pharmacol. Toxicol. 26:332-342.

Sharp, D. W., and P. C. Saunders. 1984a. Submission of unpublished data to the Environmental Protection Agency. Technical synthetic and natural pyrogallol: Comparison of the acute oral toxicity in the rat. Chesterford Park Research Station. Saffron Walden, Essex, England. (Cited by CIR, 1991)

Sharp, D. W., and P. C. Saunders. 1984b. Submission of unpublished data to the Environmental Protection Agency. Primary skin irritancy of technical synthetic and natural pyrogallol in the guinea pig. Chesterford Park Research Station. Saffron Walden, Essex, England. (Cited by CIR, 1991)

Shimoi, K., Y. Nakamura, I. Tomita, Y. Hara, and T. Kada. 1986. The pyrogallol related compounds reduce UV-induced mutations in *Escherichia coli* B/r WP2. Mutat. Res. 173:239-244.

Siage, J. 1976. Considerations on the treatment of psoriasis. Ann. Derm. Syph. 103:610. (Cited by Willsteed and Regan, 1985)

Smit, N. P. M., A. J. M. Latter, S. Naish-Byfield, W. Westerhof, S. Pavel, and P. A. Riley. 1994. Catechol-*O*-methyltransferase as a target for melanoma destruction? Biochem. Pharmacol. 48(4):743-752.

SRI Int.. 1997. Pyrogallol. In: 1997 Directory of Chemical Producers: United States of America. SRI Consulting, USA. p. 870.

Stecher, P. G. Ed. 1968. Pyrogallol. In: The Merck Index. 8th ed., Merck & Co., Inc., Whitehall, NJ. pp. 894-898.

Stenbäck, F. 1977. Local and systemic effects of commonly used cutaneous agents: Lifetime studies of 16 compounds in mice and rabbits. Acta Pharmacol. Toxicol. 41:417-431.

Stenbäck, F., and P. Shubik. 1974. Lack of toxicity and carcinogenicity of some commonly used cutaneous agents. Toxicol. Appl. Pharmacol. 30:7-13.

Stich, H. F., M. P. Rosin, C. H. Wu, and W. D. Powrie. 1981. The action of transition metals on the genotoxicity of simple phenols, phenolic acids and cinnamic acids. Cancer Lett. 14(3):251-260.

Stich, H. F., P. K. L. Chan, and M. P. Rosin. 1982. Inhibitory effects of phenolics, teas and saliva on the formation of mutagenic nitrosation products of salted fish. Int. J. Cancer 30:719-724.

Stich, H. F., S. S. Tsang, and B. Palcic. 1990. The effect of retinoids, carotenoids and phenolics on chromosomal instability of bovine papillomavirus DNA-carrying cells. Mutat. Res. 241:387-393.

Torii, Y., H. Saito, and N. Matsuki. 1994. Induction of emesis in *Suncus murinus* by pyrogallol, a generator of free radicals. Br. J. Pharmacol. 111:431-434.

van Duuren, B. L., and B. M. Goldschmidt. 1976. Cocarcinogenic and tumor-promoting agents in tobacco carcinogenesis. J. Nat. Cancer. Inst. 56(6):1237-1242.

Wang, C. Y., and J. M. Klemencic. 1979. Mutagenicity and carcinogenicity of polyhydric phenols. Proc. Am. Assoc. Cancer Res. 20:177. Abstract.

Wattenberg, L. W., P. Borchert, C. M. Destafney, and J. B. Coccia. 1983. Effects of p-methoxyphenol and diet on carcinogen-induced neoplasia of the mouse forestomach. Cancer Res. 43:4747-4751.

Willsteed, E., and W. Regan. 1985. Psoriasis, pyrogallol and skin cancer. Australas. J. Dermatol. 26(3):144-145.

Yamada, T., M. Yamamoto, and A. Tanimura. 1978. Studies on the formation of nitrosamines (VII). The effects of some polyphenols on nitrosation of diethylamine. J. Food Hyg. Soc. Jpn. 19(2):224-227.

Yamada, K., S. Shirahata, H. Murakami, K. Nishiyama, K. Shinohara, and H. Omura. 1985. DNA breakage by phenyl compounds. Agric. Biol. Chem. 49(5):1423-1428.

Yamaguchi, T. 1981. Mutagenicity of low molecular substances in various superoxide generating systems. Agric. Biol. Chem. 45(1):327-330.

Yamamoto, M., T. Yamada, K. Yoshihira, A. Tanimura, and I. Tomita. 1988. Effects of food components on the formation of nitrosamides. Food Addit. Contam. 5(3):289-298.

Yoshida, Y., M. Hirose, K. Takaba, J. Kimura, and N. Ito. 1994. Induction and promotion of forestomach tumors by sodium nitrite in combination with ascorbic acid or sodium ascorbate in rats with or without *N*-methyl-*N*' -nitro-*N*-nitrosoguanidine pre-treatment. Int. J. Cancer 56:124-128.

Yoshie, Y., and H. Ohshima. 1997. Nitric oxide synergistically enhances DNA strand breakage induced by polyhydroxyaromatic compounds, but inhibits that induced by the Fenton reaction. Arch. Biochem. Biophys. 342(1):13-21.

Zhicheng, S. 1992. Research on the Pathogenesis of Oak Leaf Poisoning in Cattle. In: L. F. James, T. L. Wierenga, B. J. Sigler, and J. A. Johnson (Eds.), Poisonous Plants: Proceedings of the Third International Symposium, Logan, UT. Iowa State University Press, Ames, IA. pp. 509-516.

Zupanovich, J. D., D. J. Sepelak, L. J. Neil, and R. K. Sinha. 1987. Method of inhibiting boiler corrosion and compositions for it. U.S. patent no. 85-801349. Abstract from CAPLUS 1987:446021.

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