International Journal of Toxicology, 26(Suppl. 3):89–118, 2007

ISSN: 1091-5818 print / 1092-874X online
DOI: 10.1080/10915810701663176

Final Report on the Amended Safety Assessment of Propyl Gallate[1]

Propyl Gallate is the n-propyl ester of gallic acid (3,4,5-trihydroxybenzoic acid). It is soluble in ethanol, ethyl ether, oil, lard, and aqueous solutions of polyethylene glycol (PEG) ethers of cetyl alcohol, but only slightly soluble in water. Propyl Gallate currently is used as an antioxidant in a reported 167 cosmetic products at maximum concentrations of 0.1%. Propyl Gallate is a generally recognized as safe (GRAS) antioxidant to protect fats, oils, and fat-containing food from rancidity that results from the formation of peroxides. Data on dermal absorption are not available, but Propyl Gallate is absorbed when ingested, then methylated, conjugated, and excreted in the urine. The biological activity of Propyl Gallate is consistent with its free-radical scavenging ability, with effects that include antimicrobial activity, enzyme inhibition, inhibition of biosynthetic processes, inhibition of the formation of nitrosamines, anesthesia, inhibition of neuromuscular response to chemicals, ionizing/ultraviolet (UV) radiation protection, chemoprotection, antimutagenesis, anticarcinogenesis and antitumorigenesis, antiteratogenesis, and anticariogenesis. Animal toxicity studies indicate that Propyl Gallate was slightly toxic when ingested, but no systemic effects were noted with dermal application. Propyl Gallate is a strong sensitizer when tested intradermally, less sensitizing when tested topically, and nonsensitizing topically at 0.1% in one study. In a second study, Propyl Gallate (15 mg dissolved in 8 ml vehicle) was sensitizing to guinea pigs. Acute eye irritation tests conducted on nine cosmetic formulations, each containing less than 1% Propyl Gallate, were negative. A phototoxicity study conducted on a cosmetic formulation containing 0.003% Propyl Gallate determined that the product was not phototoxic to guinea pigs. In one study, female rats fed 0.5 g Propyl Gallate had substantially increased fetal resorption rates when compared to controls, but in four other studies, Propyl Gallate at doses up to 2.04 g/kg was nonteratogenic in rats, rabbits, mice, and hamsters. In clinical cumulative irritancy tests, Propyl Gallate was nonirritating at concentrations up to 10%. Patch tests at concentrations less than 1% yielded positive elicitation responses. Repeat-insult patch tests using cosmetic formulations with 0.003% Propyl Gallate produced no irritation or sensitization. Propyl Gallate at a concentration of 10% in alcohol was nonphototoxic in 25 subjects. Cosmetic formulations, each containing 0.003% Propyl Gallate, produced no signs of photosensitization or phototoxicity in a total of 371 subjects. Although Propyl Gallate is not a skin irritant in clinical tests, the available data demonstrate that it is a skin sensitizer and that it may be a sensitizer at lower concentrations than originally thought, i.e., at concentrations less than 1%. In actual practice, cosmetic formulations contain Propyl Gallate at concentrations up to 0.1% and usage has increased over the past 20 years. In spite of the increased exposure associated with increased use, it is the clinical experience of the Panel that the use of Propyl Gallate in cosmetics has not resulted in sensitization reactions. Therefore, the Panel believes that a concentration limitation of 0.1% in cosmetics is necessary (given the evidence of sensitization at concentrations less than 1%) and sufficient (given that current products are not producing adverse reactions).

INTRODUCTION

The Cosmetic Ingredient Review (CIR) Expert Panel previously issued a Safety Assessment of Propyl Gallate with the conclusion that Propyl Gallate is safe as a cosmetic ingredient at concentrations not exceeding 1%. The concentration limit was based on concerns regarding dermal sensitization observed in human and animal studies (Elder 1985).

A search of the published literature identified new information regarding the safety of Propyl Gallate sufficient to reopen the report and amend the conclusion.

CHEMISTRY

Definition and Structure

As given in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), Propyl Gallate (CAS no. 121-79-9; EINECS No. 204-498-2) is the n-propyl ester of gallic acid. It conforms to the structure shown in Figure 1. Other names for this ingredient include

- 3,4,5-Trihydroxybenzoic acid propyl ester (Gottschalck and McEwen 2004),
- Propyl gallate (RIFM) (Gottschalck and McEwen 2004),
- Gallic acid propyl ester (RTECS 2004),
- n-Propyl gallate (Windholz 1976),
- PG (Windholz 1976),
- Progallin P (Windholz 1976), and
- Tenox PG (Windholz 1976).

Chemical and Physical Properties

According to the Cosmetic, Toiletry, and Fragrance Association (CTFA) *Cosmetic Ingredient Specifications* (CTFA 1972),

Received 14 May 2007; accepted 24 August 2007.

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel.

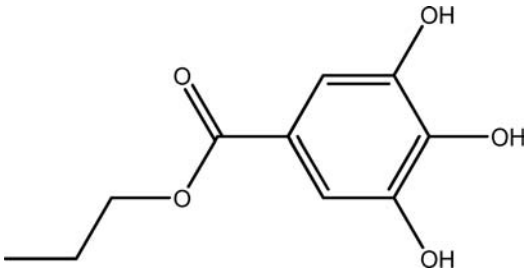

FIGURE 1
Chemical structure of Propyl Gallate (Gottshcalck and McEwen 2004).

The Merck Index (Windholz 1976), and the Japan Cosmetic Industry Association (JCIA) *Japanese Standards of Cosmetic Ingredients* (JCIA 1979), Propyl Gallate is a fine white to light brown crystalline powder with no odor and a slightly bitter taste. It is soluble in ethanol, ethyl ether, oil, and lard but is only slightly soluble in water (CTFA 1972). Propyl Gallate is also soluble in aqueous solutions of polyethylene glycol (PEG) ethers of cetyl alcohol; solubility increases as the concentration of the surfactant increases and the PEG chain length increases (Wan 1972). Boyd and Beveridge (1979) reported an octanol:water partition coefficient of 32. Table 1 summarizes these and other physical and chemical properties of Propyl Gallate.

Method of Manufacture

Propyl Gallate is the n-propylester of 3,4,5-trihydroxybenzoic acid. Natural occurrence of Propyl Gallate has not been reported. It is commercially prepared by esterification of gallic acid with propyl alcohol followed by distillation to remove excess alcohol (Food and Drug Research Labs 1972).

Analytical Methods

The literature contains many references pertaining to the determination of Propyl Gallate in foods, cosmetics, and biological systems. Chromatography is widely used for many determinations. Propyl Gallate may be analyzed directly, or it may be modified chemically and the derivative subsequently identified. Table 2 lists some of the reported analytical methods used for Propyl Gallate determination.

Reactivity

Propyl Gallate is an antioxidant. According to Boehm and Williams (1943), the antioxidant activity of Propyl Gallate resides in its hydrogen-donating hydroxyl groups. Propyl Gallate is stable in neutral or slightly acidic chemical environments but is unstable when heated or in mild alkaline environments (Bentz et al. 1952).

Gutteridge and Fu (1981) suggested that Propyl Gallate is a free-radical scavenger which may be used to prevent the free-radical ($R^{\cdot}$) peroxidation of lipids. Such free radicals can be generated by ionizing radiation, chemical reaction, oxidation, or enzymatic reactions. Lipid damage proceeds until all of the lipid is oxidized. This reaction occurs as follows:

$$\mathrm{LH\,(lipid) + R^{\cdot} \rightarrow L^{\cdot}\,(lipid\ free\ radical) + RH}$$
$$\mathrm{L^{\cdot} + O_2 \rightarrow LOO^{\cdot}\,(lipid\ peroxy\ radical)}$$
$$\mathrm{LOO^{\cdot} + LH \rightarrow LOOH + L^{\cdot}}$$

Propyl Gallate interferes with this reaction at the stage of lipid peroxy radical formation (Gutteridge and Fu 1981):

$$\mathrm{PGH\,(Propyl\ Gallate) + LOO^{\cdot} \rightarrow LOOH + PG^{\cdot}}$$
$$\mathrm{PG^{\cdot} + PGH \rightarrow PG - PG}$$

The oxidation of Propyl Gallate during free-radical

TABLE 1
Physical and chemical properties of Propyl Gallate

Property	Value	Reference
Molecular weight	212.20	Windholz 1976
Melting range	146–150°C	CTFA 1972; Windholz 1976
Absorption maximum (alcohol)	275 nm[a]	Kahn et al. 1973; Weast 1978
pK_a	8.11	Boyd and Beveridge 1979
Partition coefficient in:		
oleyl alcohol:water	17	Boyd and Beveridge 1979
octanol:water	32	Boyd and Beveridge 1979
R_m	−0.52	Boyd and Beveridge 1979
Ash	0.1% max.	CTFA 1972
Loss on drying	0.5% max.	Boyd and Beveridge 1979
Inorganic impurities[b]		
As	3 ppm max.	CTFA 1972
Pb	20 ppm max.	CTFA 1972
pH		
0.05% aqueous	6.3	Boehm and Williams 1943
0.1% aqueous	5.9	Boehm and Williams 1943
0.2% aqueous	5.7	Boehm and Williams 1943

[a]Absorption shifts to higher wavelengths at higher concentrations; increasing Propyl Gallate concentration broadens curve to 290 to 320 nm. At 10%, the absorption peak is greater than 390 nm.
[b]No information is available on organic impurities.

TABLE 2
Analytical methods used in Propyl Gallate determination

Method	Reference
Paper chromatography	Mitchell 1957; Elder 1985
Thin-layer chromatography (TLC)	Matthew and Mitra 1965; Dessel and Clement 1969
Gas chromatography (GC)	Wachs and Gassmann 1970
Vacuum sublimation/GC	McCaulley et al. 1967
Reverse-phase partition chromatography	Berger et al. 1960
Centrifugal paper chromatography	Davidek 1963
Polyamide TLC	Davidek and Pokorny 1961; Chiang and Tseng 1969
Liquid chromatography	King et al. 1980
Electron capture/gas-liquid chromatography	Page and Kennedy 1976; Kline et al. 1978
Column chromatography	Berger et al. 1960
High-performance liquid chromatography	Page 1979
Infrared spectroscopy	CTFA 1972
Fluorometric analysis	Latz and Hurtubise 1969
UItraviolet spectrophotometry	FAO/WHO Expert Committee on Food Additives 1965
Colorimetric analysis with:	
Iron (II) ion	Chatt 1962
Phosphomolybdic acid	Chatt 1962
2,2′-Bipyridyl reagent	Association of Public Analysts 1963
2,2′-Diphenyl-1-picryl hydrazyl	Elder 1985
Flow-through optosensor with solid phase UV spectroscopic detection	Capitán-Vallvey et al. 2001

scavenging shown in Figure 2 was suggested by Forgo and Buchi (1970). Sen et al. (1976) stated that this reaction occurs in the inhibition by Propyl Gallate of nitrosopyrrolidine formation in cooked, nitrite-cured bacon.

USE

Cosmetic Use

As described in the *International Cosmetic Ingredient Dictionary and Handbook*, Propyl Gallate functions as an antioxidant

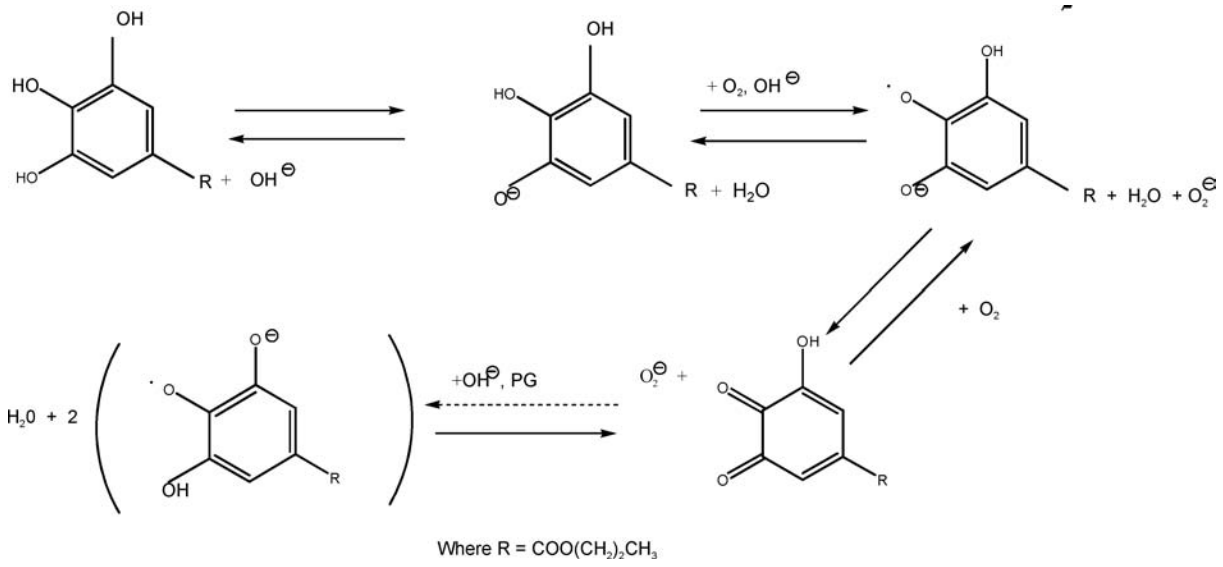

FIGURE 2
Oxidation of Propyl Gallate during free-radical scavenging suggested by Forgo and Buchi (1970).

and a fragrance ingredient in cosmetic products (Gottschalck and McEwen 2004).

More specifically, Balsam and Sagarin (1974) and Marks et al. (2002) indicated that Propyl Gallate is used as an antioxidant in cosmetics to stabilize vitamins, essential oils, perfume, as well as fats and oils, all of which readily undergo oxidation. Oxidation of these products results in rancidity, color changes, viscosity changes, and active ingredient deterioration. Oxidation can occur due to the presence of heat, light, moisture, oxygen, chemical pro-oxidants, or microorganisms. Propyl Gallate acts by inhibiting the accumulation of damaging free radicals. Propyl Gallate may be used alone but is often used in a mixture of phenolic antioxidants. Butylated hydroxyanisole (BHA) and Propyl Gallate are synergistic antioxidants.

According to the *International Cosmetic Ingredient Dictionary and Handbook*, Propyl Gallate is used in many cosmetic product categories, including lipsticks, bath preparations, miscellaneous; body and hand preparations (excluding shaving preparations); bath capsules; moisturizing preparations; skin care preparations, misc.; makeup preparations (not eye); eye makeup preparations, miscellaneous; face and neck preparations (excluding shaving preparations); bath oils, tablets, and salts; cleansing products (cold creams, cleansing lotions, liquids, and pads); eyeliners; night skin care preparations, eye shadows; eyebrow pencils; face powders; foundations; indoor tanning preparations; mascara; suntan gels, creams, and liquids (Gottschalck and McEwen 2004).

In 1981, the cosmetic industry voluntarily reported to the Food and Drug Administration (FDA) that 118 cosmetic products contained Propyl Gallate (Elder 1985). Most of these products contained $\leq$0.1 % Propyl Gallate, but the maximum concentration of use was up to 5% in fragrance powders. In 2002, industry reported 167 uses of Propyl Gallate in cosmetic products (FDA 2002). The maximum concentration was 0.1%, in the "other personal hygiene" product category (CTFA 2003). Table 3 summarizes the current and historical use and concentration data of Propyl Gallate in cosmetics as a function of cosmetic product category.

NONCOSMETIC USE

Food

Propyl Gallate has been employed as an antioxidant in foods since 1948 to protect fats, oils, and fat-containing food from rancidity, which results from the formation of peroxides. To some extent, it is used in essential oils to retard the oxidation of monoterpenes and oxidation-sensitive aldehydes and ketones. The solubility of Propyl Gallate in fats and oils is limited to less than 2%. Propyl Gallate is often difficult to dissolve in these substances without the aid of a carrier solvent (Bentz et al. 1952; Life Sciences Research Office 1973). According to Lewis (1997), Propyl Gallate functions as a food preservative and antioxidant for animal fats and oils, and is used in flavoring oils.

The Life Sciences Research Office (1973) indicated that Propyl Gallate is used at concentrations of 0.01484% to 0.00001% in fats and oils, meat products, snack foods, baked goods, nut products, grain products, frostings, chewing gum, soft candy, frozen dairy products, gelatin products, and alcoholic and nonalcoholic beverages.

The average daily intake of Propyl Gallate from foods is estimated to be 0.014 mg/kg for ages 0 to 5 months, 0.114 mg/kg for ages 6 to 11 months, 0.135 mg/kg for ages 12 to 23 months, and 0.065 mg/kg for ages 2 to 65+ years by the Life Sciences Research Office (1973).

In the Code of Federal Regulations (CFR), Propyl Gallate is listed as a generally recognized as safe (GRAS) substance (21CFR 184.1660). The FDA has placed the limit on the total antioxidant content of food at 0.02% of the fat or oil content of the food (21CFR 582.3660). Propyl Gallate may also be employed as a pressure-sensitive adhesive (21CFR 175.125).

BIOLOGICAL ACTIVITY

Absorption, Metabolism, and Excretion

Data were not available on the dermal absorption of Propyl Gallate.

Orten et al. (1948) analyzed the urine from dogs fed diets containing 0.0117% Propyl Gallate for 14 months. During this time, no detectable quantities of Propyl Gallate were found in the urine. Van Esch (1955) studied the in vivo and in vitro metabolism of Propyl Gallate. He determined that pancreatic extracts containing lipases and esterases did not hydrolyze Propyl Gallate, indicating that it was not hydrolyzed in the gut. Blood esterases also did not hydrolyze Propyl Gallate. When fed to rats, most of the Propyl Gallate was passed in the feces as the original ester. The urinary components detected were the original ester and gallic acid, and these were excreted completely within 24 h.

Booth et al. (1959) and Dacre (1960) studied the metabolism and excretion of Propyl Gallate in rats and rabbits. When Propyl Gallate was administered orally to rats, the major urinary metabolite was 4-methoxygallic acid, whereas 2-methoxypyrogallol, gallic acid, and glucuronides of the methoxylated products were the minor metabolites. When Propyl Gallate was given orally to rabbits, 79% of the administered dose was excreted in the urine, 72% as 4-methoxygallic acid glucuronide (4-methoxygalloyl-β:d-glucosiduronic acid), and 6.7% as unconjugated phenolic compounds. Minor metabolites included pyrogallol (free and conjugated) and free 4-methoxy gallic acid. Figure 3 presents the metabolic pathway of Propyl Gallate in rats and rabbits.

Antioxidant-Related Effects

Propyl Gallate inhibited eosin-sensitized photodynamic oxidation of trypsin by competing efficiently with oxygen and trypsin for reaction with the eosin triplet (excited) state. Propyl Gallate reduced the excited eosin to form a semireduced eosin radical and an oxidized Propyl Gallate form. Then, by reverse electron transfer, ground state eosin and Propyl Gallate were

TABLE 3
Current and historical uses and concentrations of Propyl Gallate in cosmetics

Product category	1981 uses (total products in the category) (Elder 1985)	2002 uses (total products in the category) (FDA 2002)	1981 concentrations (Elder 1985) (%)	2003 concentrations (CTFA 2003) (%)
Bath preparations				
Oils, tablets and salts	4 (237)	3 (143)	≤ 0.1	—
Soaps and detergents	2 (148)	2 (421)	≤ 0.1	0.000005–0.002
Eye makeup preparations				
Eyebrow pencils	—	5 (102)	—	—
Eyeliners	—	3 (548)	—	0.01
Eye lotions	—	2 (25)	—	—
Mascara	2 (397)	2 (195)	≤ 0.1	0.01
Other eye makeup preparations	—	5 (152)	—	0.03
Fragrance preparations				
Colognes and toilet waters	5 (1120)	—	≤ 0.1	0.003–0.01
Perfumes	3 (657)	—	≤ 0.1	0.002
Powders	2 (483)	1 (273)	≤ 5	—
Other fragrance preparations	—	1 (173)	—	—
Noncoloring hair preparations				
Hair conditioners	—	1 (651)	—	—
Shampoos	2 (909)	—	≤ 0.1	—
Hair tonics, dressings, etc.	—	1 (598)	—	—
Makeup preparations				
Blushers	7 (819)	3 (245)	≤ 0.1	—
Face powders	21 (555)	1 (305)	≤ 0.1	0.05
Foundations	2 (740)	2 (324)	≤ 0.1	—
Lipsticks	21 (3319)	75 (962)	≤ 0.1	0.05
Makeup bases	1 (831)	—	≤ 0.1	—
Rouges	1 (211)	—	≤ 0.1	—
Makeup fixatives	1 (22)	—	≤ 0.1	—
Other makeup preparations	7 (530)	6 (201)	≤ 0.1	0.05
Nail care products				
Cuticle softeners	1 (32)	1 (19)	≤ 0.1	—
Personal hygiene products				
Other personal hygiene products	—	2 (308)	—	0.1
Shaving preparations				
Aftershave lotions	—	—	—	0.0004
Skin care preparations				
Skin cleansing creams, lotions, liquids, and pads	9 (680)	4 (775)	≤ 0.1	—
Face and neck skin care preparations	—	5 (310)	—	—
Body and hand skin care preparations	—	12 (840)	—	0.0002
Foot powders and sprays	—	—	—	0.000005

(*Continued on next page*)

TABLE 3
Current and historical uses and concentrations of Propyl Gallate in cosmetics *(Continued)*

Product category	1981 uses (total products in the category) (Elder 1985)	2002 uses (total products in the category) (FDA 2002)	1981 concentrations (Elder 1985) (%)	2003 concentrations (CTFA 2003) (%)
Moisturizers	9 (747)	7 (905)	≤ 0.1	—
Night skin care preparations	4 (219)	4 (200)	≤ 1	—
Paste masks (mud packs)	1 (171)	—	≤ 0.1	—
Skin lighteners*	3 (44)	—	≤ 1	—
Skin fresheners	1 (260)	2 (184)	≤ 0.1	—
Wrinkle Smoothers*	1 (38)	—	≤ 0.1	—
Other skin care preparations	—	7 (725)	—	—
Suntan preparations				—
Suntan gels, creams and liquids	2 (164)	3 (131)	≤ 1	—
Indoor tanning preparations	1 (15)	4 (71)	≤ 0.1	—
Other suntan preparations	1 (28)	—	≤ 0.1	—
Total uses/ranges for Propyl Gallate	**118**	**167**	**≤1–5**	**0.000005 –0.1**

*No longer a category.

regenerated. Photodynamic activation occurred with the formation of a free radical, and Propyl Gallate acted by inhibiting free-radical formation (Rizzuto and Spikes 1975).

Propyl Gallate also inhibited mild oxidation of serum low-density lipoprotein. Upon oxidation, the apoprotein was converted from a homogeneous, high-weight substance to a mixture of low-weight polypeptides. This resulted from a reaction between the protein moiety and the autooxidizing lipid moiety of the lipoprotein. Addition of Propyl Gallate to the serum inhibited this reaction (Schuh et al. 1978).

Gonikberg et al. (1967) reported that Propyl Gallate forms a biochemical complex with flavinmononucleotide (FMN).

Antibacterial Activity

Jordan et al. (1961) studied the antibacterial effects of Propyl Gallate on bacteria of the human oral cavity. At concentrations of 0.0032% to 0.266%, Propyl Gallate inhibited the growth of 27 strains of bacteria, mostly gram positive. The authors considered this effect significant in regard to the ability of Propyl Gallate to inhibit cariogenesis. Against *Salmonella narasino* and*Saccharomyces cerevisiae*, Gallate esters were bactericidal; the effect increased as the alkyl chain length increased (Bajaj et al. 1970).

The effect of Propyl Gallate on *Escherichia coli* was further studied in 1979 by Boyd and Beveridge. The antibacterial activity of some esters of 3,4,5,-trihydroxybenzoic acid was positively correlated with its solubility, partition coefficient, pKa, and reduction of water surface tension. The authors suggested that Propyl Gallate exerts antibacterial activity by interfering with some biochemical free radical intermediate within the organism. The action was not due to uncoupling of the bacteria's oxidative phosphorylation system or damage to the cytoplasmic membrane. Propyl Gallate did inhibit respiration and malate dehydrogenase activity and altered the cytochrome spectra of treated cells, suggesting interference with the terminal cytochrome system. Propyl Gallate also inhibited synthesis of the general cell polymers, RNA, DNA, and protein.

Shih and Harris (1977) observed Propyl Gallate, at 400 ppm, to be lethal to *E. coli*, but it had little effect at this concentration on *Staphylococcus aureus*. They also observed that combinations of butylated hydroxyanisole (BHA) and Propyl Gallate were more effective than either ingredient alone, indicating a synergistic effect. They concluded, however, that at the concentrations used in foods, Propyl Gallate probably has low antimicrobial activity.

Retico et al. (1981) found that Propyl Gallate, dissolved in proplyene glycol at initial concentrations of 300 mg/ml, shows little antibacterial activity when added to the test medium. However, it potentiates the activity of meclocycline against *Pseudomanas*, *Proteus*, *E. coli*, and *Klebsiella* strains. Meclocycline was tested with Propyl Gallate in ratios of 1:8 and 1:5.33 at pH values of 5.8 and 7.2. The potentiating effect of Propyl Gallate is seen especially with resistant strains.

Chung et al. (1998) reported that Propyl Gallate at 100 to 1000 μg/ml inhibited the growth of intestinal bacterial strains *Bacteroides fragilis* ATCC 25285, *Clostridium clostridiiforme* ATCC 25537, *C. perfringens* ATCC 13124, *C. paraputrificum* ATCC 25780, *E. coli* ATCC 25922, *Enterobacter cloacae* ATCC 13047, *Salmonella typhimurium* TA98, and *S. typhimurium* YG1041.

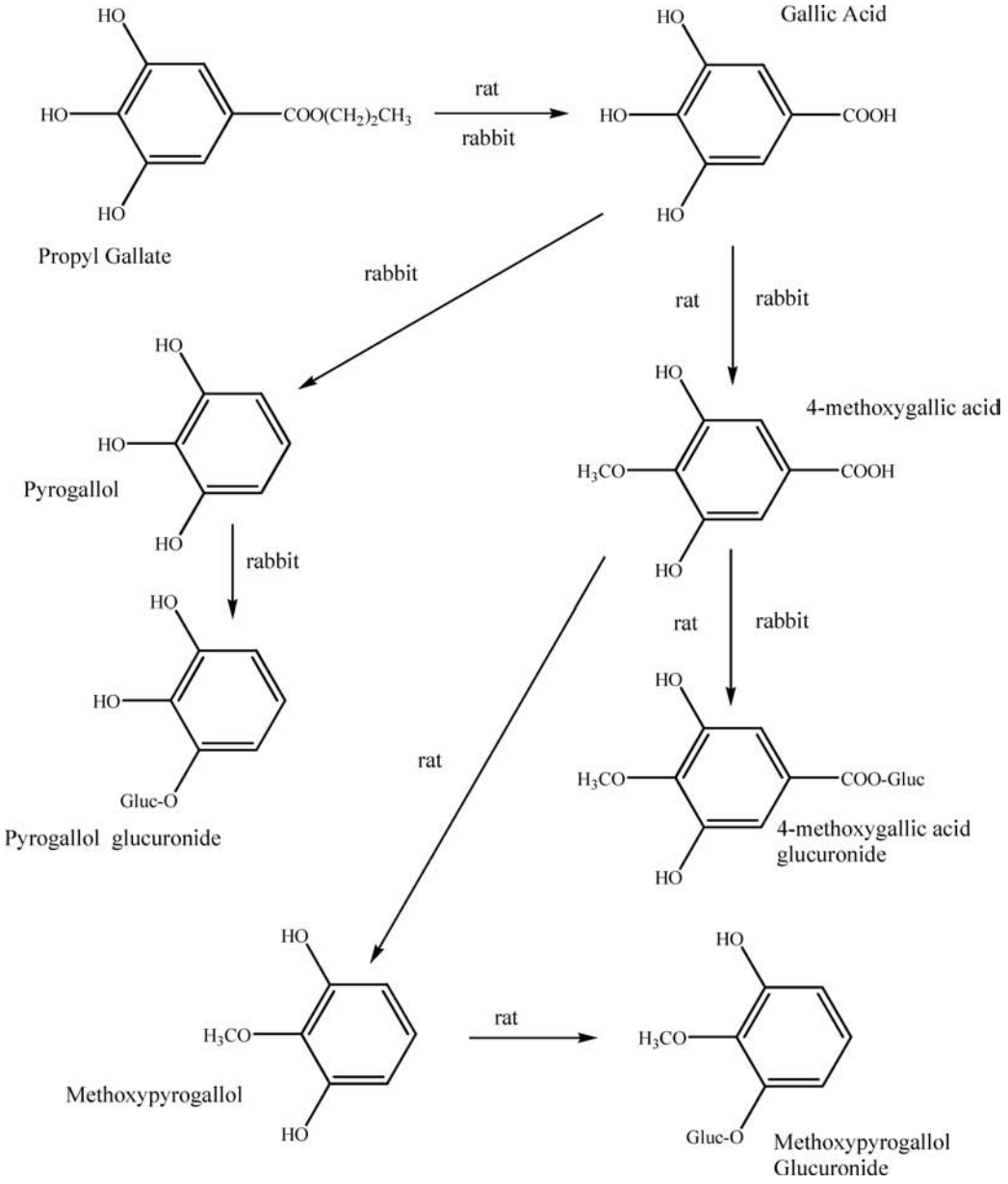

FIGURE 3
Metabolism of Propyl Gallate in rats and rabbits (after Dacre 1960).

Kubo et al. (2002) studied the anti-*Salmonella* activity of several alkyl gallates. Up to 3200 μg/ml Propyl Gallate showed no anti-bacterial activity against *S. choleraesuis*.

Antifungal Activity

Propyl Gallate stabilizes oxidation-sensitive amphotericin B and prolongs its antifungal activity. An antifungal synergism between these two compounds has been suggested (Andrews et al. 1977; Beggs et al. 1978).

Propyl Gallate increases antifungal activity of imidazole, fluconazole, and itraconazole in *Candida albicans* infections by lowering the risk of resistance to these antifungal drugs (D'Auria et al. 2001; Strippoli et al. 2000). Propyl Gallate potentiated the activity of the fungicide azoxystrobin in vitro so that resistance was no longer observed (Miguez et al. 2003).

Effects on Enzymes

Neifakh (1962) stated that free radicals are generated at almost all stages of glycolysis, respiration, oxidation, and certain enzyme systems, among other biochemical processes. Because Propyl Gallate is a free-radical inhibitor, it would be expected to affect all of these systems. Propyl Gallate decreased the

activity of certain redox enzymes, such as d-glyceraldehyde-3-phosphate dehydrogenase, lactic dehydrogenase, and alcohol dehydrogenase, all of which produce free-radical intermediates; it did not inhibit aldolase and enolase, which produce no free radicals.

Vartanyan et al. (1964) observed the inactivation of lactic dehydrogenase by Propyl Gallate was due to the oxidation of sulfhydryl (SH) groups of the enzyme by Propyl Gallate radicals (7.1×10^{-4} M). Brzhevskaya et al. (1966) reported that Propyl Gallate, at concentrations of 1×10^{-3} to 6.7×10^{-3} M, inhibited the enzymatic hydrolysis of adenosine triphosphate (ATP) 40% to 85% by blocking the formation of free radicals. Agatova and Emanuel (1966) stated that radicals of Propyl Gallate (at concentration of 1×10^{-3} M) accelerated the conversion of SH groups of enzymes to S-S bonds under oxidation. Both the formation of S-S bonds and the destruction of SH bonds deactivate enzymes. They observed that d-glyceraldehyde-3-phosphate dehydrogenase, which contains SH groups, was affected, whereas RNase and trypsin, with S-S bonds but no SH bonds, were not affected.

Propyl Gallate significantly inhibited tyrosine hydroxylase activity in vitro at concentrations of 10^{-4} to 10^{-6} M but was noninhibiting to tyrosine hydroxylase in vivo when administered intraperitoneally at 200 or 400 mg/kg in guinea pigs (Levitt et al. 1967).

Propyl Gallate inhibited microsomal aminopyrine demethylase (part of the microsomal mixed-function oxidase system) and NADPH–cytochrome *c* reductase activities. Propyl Gallate readily reacted with radical species of these systems and strongly inhibited NADPH-dependent lipid peroxidation in microsomes (Torrielli and Slater 1971).

Yang and Strickhart (1974) observed that Propyl Gallate inhibited microsomal benzo[a]pyrene hydroxylase and demethylase activities in vivo, with 50% inhibition occurring at 50 and 140 to 500 μM Propyl Gallate, respectively. Propyl Gallate did not, however, inhibit NADPH-dependent reduction of cytochrome P-450, indicating that the site of inhibition was not on NADPH-cytochrome c reductase, as Torrielli and Slater (1971) had suggested. The authors believed the site of inhibition was cytochrome P-450 itself. In 1977, Rahimtula et al. (1977) confirmed that Propyl Gallate (25 to 125 μM) did not inhibit NADPH–cytochrome P-450 reductase but did inhibit benzo[*a*]pyrene hydroxylase.

According to King and McCay (1981), conflicting in vitro results reported by Torrielli and Slater (1971) and Yang and Strickhart (1974) may mean that the concentrations of Propyl Gallate attained in vivo were much lower than those used in vitro.

Propyl Gallate inhibited three azoreductases of the hepatic microsomal mixed function oxidase system (Autrup and Warwick 1975), epoxidation of all-*trans* retinoic acid by rat tissue homogenate (Sietsem and DeLuca 1979), particulate guanylate cyclase activity from fibroblast and liver homogenates by preventing arachidonate oxidation and malonyldialdehyde formation (Ichihara et al. 1979), and glucose-6-phosphatase activity in rat microsomes both in vivo and in vitro (Paradisi et al. 1979).

Lake et al. (1980) injected Propyl Gallate (which the authors stated is metabolized to a substrate for phase II xenobiotic metabolizing enzymes (glucuronide formation) in the liver) intraperitoneally into rats daily for 7 days at a dose of 150 mg/kg per day. Animals were then killed, and homogenates obtained from the liver were analyzed for enzymic activity. Urine was analyzed daily during treatment for the presence of metabolites of D-glucuronic acid. Propyl Gallate had no effect on hepatic phase I xenobiotic metabolism (mixed-function oxidase system), cytochrome P-450, or microsomal protein content. Propyl Gallate did stimulate hepatic microsomal UDP-glucuronyltransferase activity and increased excretion of free and conjugated D-glucuronic acid.

The effect of Propyl Gallate on the hepatic mixed-function oxidase system was studied in weanling rats. Animals were placed on diets containing various quantities and types of fat plus 0% or 0.3% Propyl Gallate for 50 days. Rats were then killed, the livers were removed, and homogenates were prepared and assayed. Rats on diets containing Propyl Gallate had no significant differences in average body weights, liver weights, liver to body weight ratios, or in microsomal protein content in comparison to controls. Two hepatic microsomal mixed-function oxidases, aniline hydroxylase and amino pyrine *N*-demethylase, were unaffected by Propyl Gallate. Propyl Gallate also had no effect on cytochrome P-450 content or NADPH–cytochrome *c* reductase activity. Propyl Gallate appeared to have no in vivo influence on the rat hepatic microsomal metabolizing system (Lake et al. 1980).

Effects on Prostaglandins/Anti-inflammatory Effects

In several studies, Propyl Gallate was reported to inhibit the biosynthesis of prostaglandin (PGE) from seminal vesicles and mammary glands. Nugterin et al. (1966) were first to demonstrate that high concentrations of Propyl Gallate inhibited prostaglandin synthesis in sheep seminal vesicles. McDonald-Gibson et al. (1976) confirmed these findings (50% inhibitory concentration of 103 μM) using bull seminal vesicles in vitro. Panganamala et al. (1977) reported that Propyl Gallate, at concentrations of 4×10^{-4} M, inhibited the formation of prostaglandin from eicosa-8,11,14-trienoic acid by bovine seminal vesicle microsomes.

Propyl Gallate inhibited arachidonic acid–induced serum platelet aggregation by inhibiting serum platelet microsomal prostaglandin synthetase. Propyl Gallate did not inhibit ADP-induced platelet aggregation (Panganamala et al. 1977).

Franzone et al. (1980) studied the effect of Propyl Gallate and 2-mercaptopropionyl glycine (2-MPG) on acute inflammatory reactions and prostaglandin E_2 (PGE_2) biosynthesis. In male Wistar rats, Propyl Gallate (150 mg/kg) and 2-MPG (200 mg/kg) were administered endoperitoneally 30 min before induction

of phlogosis. The acute inflammatory reaction was triggered by injecting a mixture of carragenine, 5-hydroxytryptamine, bradykinin, and Dextran. Controls were treated with 0.9% NaCl. The animals were killed and their spleens collected.

Propyl Gallate and 2-mercaptopropionyl glycine were active in significantly inhibiting the acute inflammatory reaction in spleen samples caused by carragenine, a phlogen. In addition, the two chemicals are able to limit the biosynthesis of PGE_2. According to the authors, the anti-inflammatory effects of Propyl Gallate and 2-MPG may depend on both the scavenger properties of the two compounds against some final products of lipid peroxides (aldehydes) originated at the inflammation site and the partial inhibition of the formation of PGE_2 by acting on the cyclo-oxygenase system.

These authors also studied the effect of Propyl Gallate on prostaglandin synthetase activity of mammary gland tissue in vivo. Female Sprague-Dawley rats received diets containing various lipid content, with or without Propyl Gallate (0.3%). Rats were killed 24 h later, and homogenates of mammary gland tissues were prepared for prostaglandin synthetase activity. Dietary Propyl Gallate produced an elevation of PGF_{2a} but had no effect on PGE_2. It was suggested that Propyl Gallate scavenged the oxygen radical formed during the conversion of PGG_2 to PGH_2 and, consequently, altered the amount and types of prostaglandins produced by the mammary gland (Franzone et al. 1980).

Carpenter (1981) reported that Propyl Gallate altered prostaglandin endoperoxide synthetase and peroxidase activities of seminal vesicle microsomes. At 0.1 mM, Propyl Gallate stimulated production of PGF_{2a} and PGE_2 by mammary gland tissue microsomes, but inhibited their production at higher concentrations (0.50 to 2.50 mM). Mammary gland tissue microsomes of rats fed diets containing 0.3% Propyl Gallate synthesized more PGF_{2a} and PGI_2 than did controls. Exogenous Propyl Gallate stimulated production of PGF_{2a} and PGE_2 in rats fed control diets and rats fed vitamin E–deficient diets. The author concluded that Propyl Gallate had a concentration-dependent effect on the biosynthesis of prostaglandins by regulating the availability of lipid peroxide intermediate.

Cellular/Tissue Effects

Propyl Gallate stimulated the growth of human diploid fibroblasts at a concentration of 10^{-8} M; and inhibited their growth at concentrations of 10^{-6} M or greater (Bettger and Ham 1981). Propyl Gallate also inhibited in vitro antibody production by mouse splenic cells at 5 μg/ml and decreased multiplication of human and mouse cells at 20 μg/ml (Blalock et al. 1981).

The effect of Propyl Gallate on mouse lung metabolism was studied by Omaye et al. (1977). Groups of 16 to 24 adult mice received a single intraperitoneal injection of 0, 50, 100, or 200 mg/kg Propyl Gallate. Three days later, mice were killed, and the lungs were examined for lesions, weighed, and assayed for enzyme activity as well as DNA content. No significant pulmonary abnormalities or biochemical changes were observed in mice injected with up to 200 mg/kg Propyl Gallate.

Hepatotoxicity/Hepatoprotection

Ugazio and Torrielli (1968) studied the effect of Propyl Gallate on hepatic steatosis induced by carbon tetrachloride (CCl_4). In male Wistar rats, CCl_4 treatment caused a noticeable increase in hepatic triglyceride content within 4 h of treatment with 250 μl of CCl_4. However, when Propyl Gallate (200 mg/kg) was administered prior to CCl_4 treatment, complete protection against steatosis was observed under the experimental conditions.

Paradisi et al. (1979) determined the activity of hepatic glucose-6-phosphatase in suspensions of rat liver treated with Propyl Gallate and CCl_4 at 2.5 ml/kg. Propyl Gallate, given alone, reduced enzyme activity in a dose-dependent manner, at 12, 25, and 50 μM. The effects of CCl_4 plus Propyl Gallate, at each concentration, were additive. The authors suggested that the effect of Propyl Gallate was to interfere with the active site of glucose-6-phosphatase.

Wu et al. (1994) examined whether Propyl Gallate was a hepatoprotective antioxidant, and compared it to Trolox, a vitamin E analogue. In isolated Sprague-Dawley rat hepatocytes, Propyl Gallate substantially prolonged cell survival against oxyradicals generated with xanthine oxidase–hypoxanthine. The protection was dose dependent and excelled that of Trolox, mannitol, or ascorbate, each at or near its optimum level in the same system. Mechanistically, the authors found that Propyl Gallate (a) protected hepatocytes against the cascade of oxyradicals produced by xanthine oxidase-hypoxanthine; (b) protected hepatocytes against superoxide radicals generated specifically by menadione; (c) protected the functionally important hepatic vascular endothelial cells more effectively than Trolox against xanthine oxidase-hypoxanthine, and (d) approximately halved the amount of lipid conjugated dienes (a more specific marker of oxyradical damage than malondialdehyde) formed in tissues after oxidant damage.

The addition of Propyl Gallate (0.5 to 2.0 mM) to isolated rat hepatocyte suspension elicited concentration-dependent cell death accompanied by losses of intracellular ATP, adenine nucleotide pools, glutathione (GSH), and protein thiols. The rapid loss of intracellular ATP preceded the onset of cell death caused by Propyl Gallate (Nakagawa and Tayama 1995).

Nakagawa et al. (1996) isolated hepatocytes from fasted (18 h) rats. The addition of fructose (15 mM) to hepatocyte suspensions resulted in the prevention of Propyl Gallate (1 mM)-induced cell killing accompanied by decrease in intracellular ATP loss during a 3-h incubation period. Despite this, fructose did not completely prevent an abrupt loss of intracellular glutathione caused by Propyl Gallate, but effectively inhibited the loss of protein thiol levels.

Nakagawa et al. (1997) treated isolated rat hepatocytes with 0, 0.25, 0.50, 1.0, or 2.0 mM Propyl Gallate for 3 h. Propyl Gallate at 1 or 2 mM induced acute cell killing. At 0.5 mM,

Propyl Gallate induced signs of apoptosis. The onset of DNA fragmentation was associated with glutathione depletion.

Li et al. (1998) studied the effects of trinitrotoluene (TNT) on liver tissue of mice. Hepatocellular edema, cytoplasmic eosinophilia, and sludging of the blood with some cells undergoing particle necrosis were noted. Oral administration of Propyl Gallate concurrent with TNT exposure leads to a marked reduction in pathological change in liver tissue and clear regeneration of liver cells, demonstrating that Propyl Gallate has a certain protective effect against liver damage caused by exposure to TNT.

Gnojkowski et al. (2001) reported that Propyl Gallate (50 mg/kg, intraperitoneal [i.p.]) alone protected rat lung and kidney tissue from aryl hydrocarbonhydroxylase (AHH) activity induced by methylcholanthrene (20 mg/kg, i.p.). Propyl Gallate with octyl gallate (50 mg/kg, i.p.) had a protective effect in rat liver tissue.

Coagulant Effects

Rothwell et al. (2003) compared bandages modified by the addition of Hemostyptin, a proprietary platelet-activating reagent containing Propyl Gallate with TC-S fibrin bandages. Hemostyptin was added as an additional layer to the TC-S bandages and the bandages were tested for hemostatic efficacy in a swine femoral artery bleeding model. The TC-S + Hemostyptin preparations qualitatively and quantitatively exhibited more robust blood clotting at the surgical site than the control bandages ($p = .05$). Bleeding times were shortened for animals treated with the Hemostyptin bandages and residual platelet counts in these animals were higher.

Neurological/Neuromuscular Effects

The effect of gallates on bradykinin-induced smooth muscle contraction was studied in the isolated guinea pig ileum. When Propyl Gallate was mixed with bradykinin (a vasoactive peptide), the contractile response was suppressed. Length of the gallate alkyl side-chain influenced the degree of inhibition. The results indicated that Propyl Gallate (10^{-4} M) was a strong, partially competitive inhibitor of bradykinin; the inhibition was moderately reversible (Posati et al. 1970).

Modak and Rao (1971) studied the anesthetic activity of Propyl Gallate. Propyl Gallate was an effective anesthetic on the lumbar plexus of frogs. Infiltration anesthesia was studied in groups of 8 rabbits and guinea pigs. Propyl Gallate (1% in saline) was injected intradermally into the epilated skin of each animal. Procaine HCl was injected at other sites of the same animal to compare the response to Propyl Gallate. Pinprick reactions in these injection sites were recorded along with adverse reactions to drug injection. Onset and duration of anesthesia were also recorded.

Potentiation of Propyl Gallate's anesthetic activity by epinephrine was studied as above in each of four rabbits. Results of these tests indicated that Propyl Gallate had good local anesthetic activity when compared to a known anesthetic (Procaine). The activity of Propyl Gallate in infiltration anesthesia was potentiated by epinephrine (Modak and Rao 1971).

McDonald-Gibson et al. (1976) studied the effect of Propyl Gallate on arachidonic acid (AA)-induced abdominal contractions in mice. Treatment consisted of intraperitoneal injection, subcutaneous injection, or oral ingestion of an AA-Propyl Gallate mixture, Propyl Gallate then AA, AA then Propyl Gallate, or AA and Propyl Gallate simultaneously. Positive and negative controls were included in this study. Propyl Gallate inhibited AA-induced contractions when administered intraperitoneally as a mixture with AA (2 mg/ml incubate), as a pretreatment (4 mg/kg), or simultaneously with AA (100 μg/ml incubate). Oral and subcutaneous administration of 10 or 40 mg/kg Propyl Gallate had no effect on AA-induced contractions. The antinociceptive effect of Propyl Gallate may be due in part to its anesthetic effect and in part to deactivation of arachidonic acid.

Anticariogenesis

Jordan et al. (1961) placed rats on cariogenic diets with and without 0.5% Propyl Gallate for 90 days. Animals were then killed, and molar teeth were scored for number of caries. Positive and negative controls were included in the study. Propyl Gallate significantly decreased the number of caries per rat. At this concentration, Propyl Gallate resulted in reduced weight gains but no excessive mortality. Characteristic brown stains were observed on the surface layers of the dentin of rats on the Propyl Gallate diet; this effect was supposedly due to the formation of metal-gallate precipitates from the diet. The authors concluded that Propyl Gallate acts as an antibacterial agent in reducing caries.

Lisanti and Eichel (1963) studied the cariogenic effect in hamsters. Groups of 40 animals were fed control or cariogenic diets, which included 0% or 0.03% Propyl Gallate in the drinking water for 50 days. Animals were then killed, and teeth were scored for caries. Animals on the Propyl Gallate diet had significant weight reductions. Propyl Gallate decreased the number of caries when compared to positive and negative controls. Total number of caries was decreased by 60% in male rats and by 36% in female rats. The authors concluded that a metabolic tooth defect in this strain of animals, induced by a cariogenic diet, was partially corrected by ingestion of Propyl Gallate.

Thompson et al. (1965) reported the results of a 30-day study of Propyl Gallate in cotton rats. Groups of 16 animals received a cariogenic diet containing 0.5% Propyl Gallate for 30 days. Rats were then killed, and teeth were scored for caries. Propyl Gallate did not induce significant weight reduction in animals; it also did not decrease the incidence of caries. Propyl Gallate–fed rats had a significantly higher incidence of caries when compared to controls.

Ionizing/Ultraviolet Radiation Protection

Ionizing radiation results in excessive peroxide formation in animal tissue; these peroxides are, in turn, tissue damaging. In mice administered Propyl Gallate orally (0.25% to 0.5% in the

diet) or intraperitoneally (30 to 150 mg/kg) and in rats administered Propyl Gallate intraperitoneally (50 mg/kg) prior to exposure to sublethal doses of radiation, a protective effect was observed (Ershoff and Steers 1960; Gorodetskii et al. 1962; Lipkan et al. 1962; Isupova and Balabukha 1963).

Propyl Gallate inhibited DNA depolymerization induced by ionizing radiation in vitro (Gorodetskii et al. 1961; Lipkan et al. 1962; Isupova and Balabukha 1963; Emanuel et al. 1960). Pre- or post-treatment with Propyl Gallate increased the survival rate of monkey heart cells in vitro following gamma-radiation (Parkkhomenko 1963). Sheng et al. (1982) found radiation-induced spins could be transferred from DNA to Propyl Gallate and believed it was exclusively due to a hydrogen transfer mechanism.

Propyl Gallate inhibited lipid peroxidation in lysosomal membranes treated with high-energy radiation in vitro (Williams and Slater 1973). This result prompted Kahn et al. (1973) to study the photoprotective effect of Propyl Gallate in two in vitro systems, photohemolysis of red blood cells (RBCs) and growth inhibition of *Candida albicans* by light. Propyl Gallate protected RBCs from ultraviolet light (280 to 370 nm) via energy absorption and significantly reduced the oxygen tension of the system (photohemolysis is inhibited by decreased oxygen tension). Propyl Gallate did not protect *C. albicans* from the deleterious effects of radiation. As a photoprotector, Propyl Gallate may act by reducing the formation of free radicals during radiolysis of tissue water, which reacts with membrane lipids to produce damaging lipoperoxides, or it may act as a free-radical scavenger to neutralize free radicals formed by hydrogen donation.

Propyl Gallate (0.3 to 1 mg/ml) protected *S. typhimurium* against the lethal and mutagenic effects of gamma-radiation in the presence of oxygen. The magnitude of protection in each case was similar. No protection occurred when Propyl Gallate was added immediately after radiation (Ben-Hur et al. 1981).

The effect of Propyl Gallate as an ultraviolet light protector was studied in vivo by McDonald-Gibson and Schneider (1974). The test material (up to 10% w/w) was applied to the epilated ear of guinea pigs either before or after ultraviolet (UV) radiation. In unprotected sites, radiation resulted in erythema, edema, and blister formation. Pretreatment with Propyl Gallate inhibited induction of erythema, edema, and pyresis. Post treatment inhibited blister formation. In a similar study, Propyl Gallate (3 to 15 mg/animal) was applied under occlusion to male rat epilated dorsal skin immediately after radiation with a Hanovia Model 10-quartz lamp (with filter) emitting UV light greater than 295 nm. Erythema was assessed 4 h later. When compared to control sites, Propyl Gallate reduced UV light–induced erythema. This effect may be linked to its inhibition of prostaglandin synthesis (Law and Lewis 1977).

Chemoprotection

Propyl Gallate, in doses ranging from 30 to 300 mg/kg body weight, inhibited the toxic effects of certain chemicals in rats. These chemicals, through the formation of free radicals, can result in lipoperoxidation (CCl_4), hepatotoxicity (acetaminophen), fatty liver (white phosphorus, CCl_4), hepatic polysomal disaggregation (white phosphorus), hemolysis of RBCs (vitamin D_2), and decreased hepatic microsome amino acid incorporation (CCl_4). Propyl Gallate acted as a free-radical scavenger and inhibited lipoperoxidation. It also inhibited cytochrome P-450 of the microsomal mixed-function oxidase drug-metabolizing system; this resulted in decreased formation of potentially toxic metabolites (Dianzani and Ugazio 1973 ; Gravela et al. 1971; Slater and Sawyer 1971; Torrielli and Ugazio 1975; Spirichev and Blazhevich 1968; Dianzani 1972; Pani et al. 1972; Astill and Mulligan 1977; Kelleher et al. 1976).

In a study of the antioxidant effects of Propyl Gallate, the survival rate of mice exposed to 8 ppm phosgene for 20 min in a whole-body exposure chamber was increased when the animals were pretreated with 0.75% Propyl Gallate in the food for 23 days. This protective effect was not seen following pretreatment with 1.5% Propyl Gallate and the authors suggested this may relate to a ceiling for effective dietary supplementation with Propyl Gallate (Sciuto and Moran 2001).

ANIMAL TOXICOLOGY

Acute Effects

Oral Toxicity

The acute oral LD_{50} of Propyl Gallate has been determined in mice (1.70 to 3.50 g/kg), rats (2.1 to 7 g/kg), hamsters (2.48 g/kg), and rabbits (2.75 g/kg). Groups of animals received the test material at one or more doses, orally or by gastric intubation. Animals were observed for up to 10 days. In a number of studies, the tissues from animals that died were examined microscopically. Results of these tests are summarized in Table 4.

Three lipstick formulations containing Propyl Gallate were evaluated in a rat acute oral toxicity study. The test material was given by gastric intubation. No deaths occurred in the separate tests of two lipstick formulations (doses up to 5.0 g/kg) containing 0.005% Propyl Gallate (Stillmeadow 1977a, 1977b). A third formulation, containing less than 1% Propyl Gallate, produced diarrhea in the test animals at all doses up to 10 ml/kg of the formulation. No deaths occurred at any dose. No lesions were found in the test animals at necropsy (CTFA 1980d).

A sun protection stick and a suntan cream, each containing 0.003% Propyl Gallate, were administered by gavage to 10 rats in acute oral toxicity studies. The sun protection stick was administered as a 50% solution in olive oil at a single dose of 25 g/kg, and the suntan cream was administered full strength at a single dose of 50 ml/kg. Rats were observed for 14 days; no deaths or toxic effects resulted from the administration of either suntan preparation. The investigators concluded that the sun protection stick and suntan cream were practically nontoxic and nontoxic, respectively (CTFA 1976, 1977).

TABLE 4
Acute oral toxicity of Propyl Gallate

Animal	Number/group	Dose levels	LD_{50}	Toxicity classification	Reference
Mouse	6–10	1–4 g/kg	2.00 g/kg	Slightly toxic	Boehm and Williams 1943
Mouse	Not given	Not given	3.50 g/kg	Slightly toxic	Lehman 1950
mouse	Not given	0.5–2.5 g/kg	1.70 g/kg	Slightly toxic	Karplyuk 1959
mouse	Not given	Not given	2.85 g/kg	Slightly toxic	Life Sciences Research Office 1973
Rat	2–18	2–5 g/kg	3.8 g/kg	Slightly toxic[a]	Orten et al. 1948
Rat	Not given	Not given	5–7 g/kg	Practically nontoxic[b]	Van Esch 1955
Rat	Not given	0.5–2.5 g/kg	2.60 g/kg	Slightly toxic	Karplyuk 1959
Rat	Not given	Not given	3.60 g/kg	Slightly toxic	Dacre 1960
Rat	Not given	Not given	2.50 g/kg	Slightly toxic	Daniyalov 1966
Rat	Not given	Not given	3.00 g/kg	Slightly toxic	Life Sciences Research Office 1973
Rat	5	0.1–4.0 g/kg	2.1 g/kg	Slightly toxic[c]	Litton Bionetics 1974
Rat	10	5 g/kg	>5 g/kg	Practically nontoxic[d]	Litton Bionetics 1974
Rat	Not given	Not given	4 g/kg	Slightly toxic	Tanaka et al. 1979
Hamster	Not given	Not given	2.48 g/kg	Slightly toxic	Life Sciences Research Office 1973
Rabbit	Not given	Not given	2.75 g/kg	Slightly toxic	Life Sciences Research Office 1973
Pig	Not given	2–6 g/kg	>6 g/kg	Practically nontoxic[d]	Van Esch 1955

[a] Deaths due to asphyxia or cardiorespiratory failure; autopsy revealed dilatation of visceral and peripheral blood vessels and inflated lungs.
[b] Kidney damage seen in dead animals.
[c] Pleural fluid and distended intestines seen in dead animals.
[d] No deaths.

Intraperitoneal Toxicity

The acute i.p. toxicity of Propyl Gallate was studied in rats. Groups of 2 to 18 animals received single IP injections of 0.2 to 0.5 g/kg Propyl Gallate. The acute i.p. LD_{50} was determined to be 0.38 g/kg. Death usually occurred within 10 to 60 min post injection and appeared due to asphyxia or cardiovascular failure. Necropsies of animals that died revealed dilatation of visceral and peripheral blood vessels, especially those leading to the adrenal glands, and inflated lungs (Orten et al. 1948).

Dermal Irritation

Table 5 presents a summary of acute dermal irritation data. Propyl Gallate was practically nonirritating to rabbit and guinea pig skin in five tests using concentrations as high as 10% (in propylene glycol) and as low as 0.003% (in a formulation).

In a study by Boehm and Williams (1943), a 10% solution of Propyl Gallate in propylene glycol was applied to the shaved intact skin of guinea pigs for 48 hours. No local lesions or primary irritation were observed.

Modak and Rao (1971) injected Propyl Gallate, at concentrations of 0.5% and 1.0% in saline, intradermally into the shaved skin of each of three albino rabbits. Positive and negative controls were included in the study. Ten minutes later, 10 mg/kg Trypan blue were administered intravenously. Treated sites were observed 1.5 hours later for tissue irritation (based on the amount of tissue coloration). Propyl Gallate at 0.5% and 1.0% resulted in a mean irritation score of 2 (maximum score = 16). The authors concluded that Propyl Gallate was practically nonirritating.

As reported by CTFA (1980a), a primary skin irritation test on the intact and abraded skin of 6 rabbits was conducted using a lipstick formulation containing less than 1% Propyl Gallate. The test material was applied for 24 h under an occlusive wrap. Upon removal of the wrap, the test sites were scored for erythema and edema at 24 and 72 h. No erythema was observed. A very slight edema at three intact and three abraded sites and a slight edema at one abraded site were observed at 24 hours, but none at 72 hours. The formulation gave a primary irritation index (PII) of 0.33 and was not considered a primary irritant.

A primary skin irritation test (CTFA 1977a) was conducted to evaluate a suntan cream containing 0.003% Propyl Gallate. Test samples weighing 0.5 g were applied to the intact and abraded skin of each of six rabbits. Sites were washed and rinsed after 24 h and reactions scored 30 min later. This procedure was repeated for three applications. Five rabbits had grade 1 erythema (scale of 0 to 4) at the 48- and 72-h readings; no edema was reported. The suntan cream was not considered a primary skin irritant.

A modified Draize skin irritation test (CTFA 1980b) was performed to evaluate a suntan oil containing 0.003% Propyl Gallate. Test samples of 0.5 ml were applied to the shaved skin of each of six rabbits. Sites were washed and rinsed after 6 h and reactions scored 30 min later. Similar applications were made on the following 2 days. Average scores of 1 (scale of 0 to 8)

TABLE 5
Acute dermal irritation of Propyl Gallate

Material tested	Type of test	Animals	Results/comments	Reference
Propyl Gallate at 10% in propylene glycol	Applied to shaved skin for 48 h	Unspecified no. of guinea pigs	No local lesions or primary irritation	Boehm and Williams 1943
Propyl Gallate at 0.5% and 1.0% in saline	Intradermal injection	3 rabbits	Score of 2 (max. = 16); practically nonirritating	Modak and Rao 1971
Propyl Gallate at 0.003% in a suntan cream	Primary skin irritation test on intact and abraded skin; 3 24-h applications	6 rabbits	5 rabbits exhibited grade 1 (max score of 4) erythema at 48 and 72 h; no edema; not a primary skin irritant	CTFA 1977a
Propyl Gallate at <1% in a lipstick	Primary skin irritation test on intact and abraded skin; 24-h application	6 rabbits	PII = 0.33 (max = 8); not a primary irritant	CTFA 1980a
Propyl Gallate 0.003% in a suntan oil	Primary skin irritation test on intact skin; three 6-h applications	6 rabbits	One score of 1 (max. score of 8) at 48 and at 72 h; practically nonirritating	CTFA 1980b

were found in one rabbit at 48 h and 1 at 72 h. The suntan oil was practically nonirritating under the test conditions.

Acute Ocular Irritation

As shown in Table 6, Propyl Gallate was nonirritating to rabbit eyes in nine tests of cosmetic formulations containing less than 1% Propyl Gallate.

An acute eye irritation test on six rabbits was conducted using a lipstick formulation containing less than 1% Propyl Gallate. The left eye received 0.1 ml of the test formulation; the right eye was untreated and served as a control. A mild conjunctival erythema in one rabbit was reported. The latter was graded as a response of 2 (maximum score of 110). The lipstick formulation was not considered an eye irritant (CTFA 1980c).

Two suntan preparations, a sun protection stick and a suntan cream, each containing 0.003% Propyl Gallate, were tested for acute eye irritation by the Draize technique (Draize 1959). A 0.1-g sample of each product (full strength) was instilled into the conjunctival sac of nine rabbits. Three rabbits received no further treatment, the eyes of the second three were rinsed with water 2 s after instillation, and the eyes of the third three were rinsed 4 s after instillation. Reactions were scored at 24, 48, and 72 h, and 4 and 7 days. Six of the nine rabbits receiving the sun protection stick had conjunctival irritation (1+ on a scale of 0 to 3) at 24 h. Only two rabbits had conjunctival irritation at 48 h, and all eyes were clinically normal at 72 h. Five of the nine rabbits receiving the suntan cream had conjunctival irritation (1 on a scale of 0 to 3), and two had chemosis (1 on a scale of 0 to 4) at 24 h. All eyes were normal at 48 h. The products were not considered eye irritants (CTFA 1977c, 1977d).

Six cosmetic formulations, each containing 0.003% Propyl Gallate, were tested according to the Consumer Product Safety Commission (CPSC) test for eye irritants as described in the Code of Federal Regulations (16 CFR 1500.42). Six rabbits were used to evaluate each formulation; one eye of each rabbit received a 0.1-ml sample of the product and the other eye served as a control. One group of six rabbits also served as an untreated control. Reactions were scored on a standard Draize scale at 24, 48, and 72 h and 7 days. The formulations produced no or very slight irritation, all of which progressively decreased

TABLE 6
Acute ocular irritation—product tests

Product	Concentration of Propyl Gallate	Test	Animals	Findings	Reference
Sun protection stick	0.003%	Draize	9 rabbits	Nonirritant	CTFA 1977c
Suntan cream	0.003%	Draize	9 rabbits	Nonirritant	CTFA 1977d
Lipstick	<1%	Draize	6 rabbits	Nonirritant	CTFA 1980c
6 cosmetic formulations	0.003%	CPSC test for eye irritants	6 rabbits	Nonirritants	CTFA 1981a, 1981b

to a 0 score at 72 h. None of these formulations were considered eye irritants (CTFA 1981a, 1981b).

Subchronic Effects

Oral Toxicity

Rats and pigs (strain/breed and number not specified) were fed diets containing 0.035% to 0.5% and 0.2% Propyl Gallate, respectively, for 3 months. Animals were then killed and necropsied. Propyl Gallate, at the concentrations tested, had no effect on growth, reproduction, organ weights, blood chemistry values, morphology of blood cells, or histopathologic changes of tissues of treated animals when compared to controls (Van Esch 1955).

Propyl Gallate was included in the diets of mice and rats at doses of 170 and 340 mg/kg (mice) or 260 and 520 mg/kg (rats) for 2.5 months. Ingestion of Propyl Gallate resulted in decreased growth rates as well as reductions in serum catalase, peroxidase, and cholinesterase activities (Karplyuk 1959).

Six groups of 12 weanling rats each were fed diets containing 0% to 0.5% Propyl Gallate for 6 weeks. Animals were then killed, blood samples were collected and analyzed, liver and adrenal glands were examined microscopically, and total lipid content of the liver was determined. Propyl Gallate had no significant effect on growth rate at any dose. Liver and adrenal gland weights were normal, and no pathologic changes could be attributed to treatment. Propyl Gallate did not produce significant toxic effects in rats when ingested and was considered safe for use in food (Johnson and Hewgill 1961).

Propyl Gallate, fed to rats for 1 or 3 months, did not affect development of enterokinase in the mucosa of the upper portion of the small intestine, nor did it affect pancreatic lipolytic enzyme secretion (Karplyuk 1968).

Feuer et al. (1965) administered doses of 0 to 500 mg/kg per day Propyl Gallate by gavage for 1 week to four groups of eight rats each and one group of seven rats. Animals were killed 24 h after the final dosing. Four additional groups of six rats each were maintained at the high dose (500 mg/kg per day) and killed 14 and 28 days after the last dosing. Histopathological examination and biochemical analyses were performed on the liver of all animals. Positive (carbon tetrachloride) and negative (arachis oil) controls were included in the study.

Propyl Gallate had no effect on hepatic weight or on hepatic enzymic activity. Slight fatty change was observed in the liver of rats given 100, 200, and 500 mg/kg per day. This effect was not dose dependent and not statistically significant. At the highest dose, extensive fatty change was observed 24 h after the final dosing, but the severity decreased significantly after 14 days of recovery. By 28 days, the livers of most animals had returned to normal. Propyl Gallate also significantly increased the number of abnormal mitotic figures in hepatocytes. At the highest dose tested, this effect persisted throughout the first 14 days of the recovery period but had disappeared by the 28th day post treatment (Feuer et al. 1965).

The National Toxicology Program (NTP) conducted a 14-day study to determine the doses of Propyl Gallate to be used in a 2-year study of carcinogenicity (NTP 1982). Groups of five male and five female F344/N rats and B6C3F1 mice were fed diets containing 6000, 12,500, 25,000, 50,000, or 100,000 ppm Propyl Gallate for 14 days. No controls were used. Animals were observed twice daily for mortality and weighed weekly. Necropsies were performed on all animals. All rats receiving 100,000 ppm Propyl Gallate died, and one male receiving 50,000 ppm died. Male rats administered 50,000 ppm lost weight. Weight gain by female rats receiving 50,000 ppm was less than 25% of that for groups receiving lower doses. However, feed consumption by male rats fed 50,000 was comparable with that of rats fed lower doses. All mice receiving 100,000 ppm and 4/5 males and 5/5 females receiving 50,000 ppm died. Mean body weight gains by dosed male and female mice were inversely proportional to dose.

The NTP also conducted a 13-week study to evaluate the cumulative toxicity of Propyl Gallate. Groups of 10 rats of either sex were fed diets containing 0, 1500, 3000, 6000, 12,500, or 25,000 ppm Propyl Gallate. Groups of 10 mice of either sex were fed diets containing 0, 800, 1500, 3000, 6000, or 12,500 ppm. Animals were observed twice daily for mortality and individual animals were weighed weekly.

At the end of the 13-week study, survivors were killed with carbon dioxide. Necropsies were performed on all animals not autolyzed or cannibalized.

One female rat receiving 12,500 ppm and one control female died. Males receiving 12,500 or 25,000 ppm and females receiving 25,000 ppm had weight gain depressions of 10% or more when compared with weight gains for controls. All rats administered 25,000 ppm had dirty tails, indicative of digestive tract disturbances.

For rats, the duodenal mucosa was reddish in 8/10 males and 6/10 females fed diets containing 25,000 ppm Propyl Gallate and the stomach wall was thickened in 4/10 males and 2/10 females receiving 25,000 ppm. At this same dietary concentration, necrosis and ulceration of the mucosal surface of the stomach and a moderate to severe granulomatous inflammatory response in the submucosa and muscular wall of the stomach were observed in 4/10 males and 1/10 females. No stomach or duodenal lesions were observed during histopathologic evaluations of male and female rats in the 6000 and 12,500 ppm dose groups. No mice died. Weight gain in the dosed groups could not be evaluated because controls were dehydrated as a result of a malfunction in the watering system during the experiment. No compound-related gross or microscopic lesions were observed (NTP 1982).

Dermal Toxicity

Dermal toxicity was studied using Propyl Gallate, 20% in lanolin, applied daily, five times per week for 6 weeks to the ears of 53 male guinea pigs. Skin biopsies were performed weekly during treatment and at 4-day intervals for 2 weeks after

discontinuation of treatment. Tissues were prepared for electron microscopy. Treatment with Propyl Gallate resulted in reversible hyperplasia of the epidermis (Riley and Seal 1974).

The effect of Propyl Gallate on skin depigmentation was studied in black guinea pigs. The test material was applied daily for 1 to 6 months at concentrations of 0.1% to 10% to the epilated dorsal skin of groups of two to five animals. Positive (monomethyl ether of hydroquinone and tertiary butyl catechol) and negative (solvent) controls were also used. Depigmentation and irritation were assessed regularly; punch biopsies were also taken and examined microscopically. Propyl Gallate induced some irritation but did not result in depigmentation (concentration not stated) (Gellin et al. 1979).

Chronic Oral Toxicity

Orten et al. (1948) fed 10 groups of 10 to 20 weanling albino rats diets containing either 0% or 0.00117% to 2.34% Propyl Gallate, or an antioxidant mixture containing 2% Propyl Gallate for 2 years. Some animals were killed at various times throughout the study; these animals, along with animals that died, were necropsied. Growth, blood parameters, organ weights, and histopathological changes were monitored.

Rats given 1.17% or 2.34% Propyl Gallate had significantly reduced growth rates, but growth of rats at lower concentrations was similar to controls. When the concentration of Propyl Gallate was decreased for these animals, growth returned to normal. No other gross effects were observed. Animals of the 1.17% and 2.34% Propyl Gallate groups had significantly decreased hemoglobin values and erythrocyte counts. The only consistent abnormalities observed upon necropsy were mottled kidneys. On microscopic examination, tubular damage and the presence of albuminous casts were found in animals of the 1.17% and 2.34% groups. Rats fed these concentrations also had significantly higher mortality rates.

These authors also fed two groups of 20 guinea pigs each (14 males and 6 females) diets containing 0% or 0.0117% Propyl Gallate for 14 to 15 months. Males and females were mated within each group after 1 year of feeding; six offspring were observed for 2 months following birth. Animals were observed and killed, and biological parameters were monitored. Propyl Gallate had no effect on growth rate, appearance, or reproduction. No abnormalities were found at necropsy or at histopathological examination of organs of Propyl Gallate–treated guinea pigs.

In addition, two groups of five and seven dogs were fed diets containing 0% and 0.0117% Propyl Gallate, respectively, for 14 months. No alterations in behavior, appearance, or physical activity, as well as blood and urinary parameters, were found. The results indicated that, at the dose tested, Propyl Gallate did not change renal or hepatic function (Orten et al. 1948).

Lehman et al. (1951) studied the effect of Propyl Gallate on mortality in rats. Six groups of 16 animals each were fed diets containing 0% to 5% Propyl Gallate for 2 years. Animals were killed at various times throughout the study and were necropsied along with deceased animals. None of the treated groups had significant differences in the number of animals surviving after 2 years of feeding when compared to controls. The only significant pathological finding was patchy hyperplasia in the stomach of rats fed the 5% Propyl Gallate diet. Propyl Gallate was concluded to be safe for use in foods.

Graham et al. (1954) fed seven groups of 26 rats each diets containing bread made with various concentrations of antioxidants, resulting in effective concentrations of 0, 0.405, or 20.25 mg Propyl Gallate per kg diet. Rats were maintained on the diets for 1 year. Food consumption, body weight, mortality, appearance, and behavior were monitored. At 13 and 26 weeks, three rats of each sex from each group were killed and necropsied, and tissues were examined microscopically, as were all animals that died during the experiment. At the conclusion of the feeding study, the remaining animals were killed and necropsied. Propyl Gallate had no significant effects on growth rates or organ weights. A low incidence of renal tubular degeneration and glomerulonephritis was observed in Propyl Gallate–treated female rats.

In a subsequent study, Graham and Grice (1955) added the bread ingredients at the same doses directly to the basal diet of 14 groups of 15 rats each for 32 weeks instead of baking the bread ingredients prior to addition to the diet. No significant differences in body weight, hematological parameters, organ lesions, appearance, behavior, mortality, or organ weights were found attributable to the ingestion of up to 20.25 mg Propyl Gallate per kg diet.

Van Esch (1955) fed diet containing 0.035% to 0.5% and 0.2% Propyl Gallate to groups of rats and pigs (strain/breed unspecified) for more than 3 months until a few litters had been produced. All animals were then killed and necropsied. Propyl Gallate induced no significant changes in growth or reproduction. No significant abnormalities attributed to ingestion of Propyl Gallate were observed at necropsy. In older rats at 0.035% Propyl Gallate and in a 'few" controls, calcium deposits and tubular protein casts were found in the kidneys. These changes were not observed in rats fed higher concentrations of Propyl Gallate and were considered unrelated to the administration of Propyl Gallate. In rats and pigs on the 0.035% Propyl Gallate diet, organ weights and hematologic values did not differ significantly from controls.

In a chronic feeding study, groups of 46 rats were fed diets containing either a mixture of food additives including Propyl Gallate or no additives. In the mixture, the dose of each compound was 35 times the average daily human consumption. There were no differences in weight gain, fertility, or survival between control and test animals (Tarjan et al. 1965).

A mixture of the antioxidants butylhydroxyanisole and Propyl Gallate, at a ratio of 2:1 (butylhydroxyanisole 20 mg/kg, Propyl Gallate 10 mg/kg), at 100 times exaggeration with its prolonged feeding to male and female white rats (type unspecified), increased mortality of experimental animals compared to those fed normal feed (Daniialov 1966).

Dacre (1974) fed three groups of 50 albino mice each diets containing 0%, 0.5%, or 1.0% Propyl Gallate for 90 weeks. Body weights, feed consumption, and hematological parameters were monitored. All surviving mice were killed at 21 months and necropsied. No significant toxic effects were observed. No significant differences in body weight, growth, gross abnormalities, or hematological parameters were observed between test and control animals. The author noted that the 1% intake of Propyl Gallate corresponded to a dose of 1.5 g/kg per day, whereas the no-effect level reported by Orten et al. (1948) corresponded to an intake of 0.05 g/kg per day.

Dermal Sensitization

Kahn et al. (1974) conducted three separate tests to determine the sensitizing potential of Propyl Gallate in guinea pigs. In the first test, Propyl Gallate (5% in complete Freund's adjuvant) was administered intradermally every other day for 6 days into the clipped dorsal skin of two female guinea pigs. Ten days after the last injection, occlusive patches containing 0.1%, 0.5%, and 2% Propyl Gallate in alcohol were each applied to the clipped ventral skin for 24 h. Sites were scored at 24 and 48 h. No sensitization occurred at 0.1%, but it did occur at the other two test concentrations. Reactions gradually subsided within 7 to 10 days. Tests performed 3 months later (dose unstated) using these sensitized guinea pigs gave similar responses. There was no cross-sensitivity with pyrogallol, gallic acid, or methyl gallate; there was weak cross-sensitivity with lauryl gallate.

In the second study, 20% Propyl Gallate in alcohol was applied for 24 h under occlusion to clipped shoulder skin of two guinea pigs every third day for 9 days. Two weeks after removal of the final induction patch, occlusive challenge patches containing 0.1%, 1%, or 5% Propyl Gallate were applied to the clipped ventral skin for 24 h. Sites were scored at 24 and 48 h. Mild to moderate irritation was produced by 1% and 5% Propyl Gallate at 24 h and by 5% at 48 h. No reactions were seen for 0.1%. When animals were retested 3 months later (dose unspecified), severe reactions were observed.

In the third study, 10% Propyl Gallate in alcohol and olive oil was administered orally to a group of 4 guinea pigs daily for 7 consecutive days. Two weeks later, the animals were given intradermal injections of 5% Propyl Gallate and 0.05% dinitrochlorobenzene (DNCB) in complete Freund's adjuvant into the clipped dorsal skin, every other day for 6 days. Additionally, a group of two animals received the intradermal injections but did not participate in the Propyl Gallate feeding induction. Ten days after the final injection, 24-h occlusive challenge patches containing 0.1%, 0.5%, or 2% Propyl Gallate and 0.1%, 0.05%, or 0.01% DNCB were applied to previously untested skin sites.

Sites were scored at 24 and 48 h. None of the Propyl Gallate-fed animals reacted to Propyl Gallate challenge patches, but all animals reacted to challenge with DNCB. Guinea pigs not orally dosed with Propyl Gallate developed mild or moderate to severe irritation to challenge patches containing 0.5% or 2% Propyl Gallate, respectively. At 0.1%, Propyl Gallate was nonsensitizing. The authors concluded that Propyl Gallate was a strong sensitizer when given intradermally. By the cutaneous route, it was less sensitizing and required a much longer induction time. Specific tolerance to Propyl Gallate-induced contact sensitization occurred following ingestion (Kahn et al. 1974).

Hausen and Beyer (1992) used the guinea pig sensitization assay to study the propyl, octyl, and dodecyl (lauryl) gallate. Sensitization was carried out using 15 mg of the pure gallate. Female guinea pigs were used in groups of 10. On days 1, 5, and 9, an emulsion was prepared consisting of 4 ml physiological saline and 4 ml Freund's Complete Adjuvant, in which the gallate was dissolved. Intradermal injections of 6×0.1–0.15 ml of this emulsion were made in a semicircular arc on the clipped and shaved shoulder area from left to right. The animals rested for 11 days and were challenged on day 20.

The challenge was performed by applying 0.05 ml of subirritant doses of the gallates to the shaved right flank of the animals. Each compound was dissolved in a 0.02 M concentration in acetone. Elicitation of cross-reactions was done on day 26 on the opposite flank. For elicitation of cross-reactions, the gallates were used at 1% and 0.1%. The tests were read at 24, 48, and 72 h. All gallates tested were moderate to strong contact sensitizers, with dodecyl being the strongest. A correlation between side chain length and mean response was observed, giving a maximum of sensitization at a length of 12 carbon atoms.

Ashby et al. (1995) exposed mice for 3 consecutive days to 5%, 10%, and 25% Propyl Gallate in acetone/olive oil (80/20, v/v) on the dorsum of both ears for the local lymph node assay. The induction phase of skin sensitization is associated with, and dependent upon, the initiation of T-lymphocyte responses in lymph nodes draining the site of exposure. Five days following initiation of exposure, mice were injected intravenously with [^{3}H]thymidine and activity was measured as a function of isotope incorporation in draining auricular lymph nodes. The authors classified any chemical which provoked a three-fold or greater increase in isotope incorporation compared with vehicle-treated controls at one or more concentration as potential sensitizers. The authors admitted this criterion was arbitrary but was based on experience with the assay. Propyl Gallate was found to be active in the local lymph node assay.

Phototoxicity

A phototoxicity test was used to evaluate a sun protection stick containing 0.003% Propyl Gallate. The product was applied full strength to one of the tape-stripped ears of each of six guinea pigs, the untreated ears serving as controls. One positive control with 8-methoxypsoralen and one unirradiated control with the sun protection stick were also maintained. Each guinea pig was exposed for 2 h to UVA from two GE F8T5-BL lamps at a distance of 4 to 6 cm. Ears were evaluated for irritation 24 and 48 h later. No irritation was seen in any of the six guinea pigs.

The sun protection stick was not phototoxic under these test conditions (CTFA 1977e).

GENOTOXICITY

Litton Bionetics (1974) used three different assays, a host-mediated assay, a cytogenetic assay, and a dominant lethal assay, to evaluate the mutagenicity of Propyl Gallate.

The host-mediated assay consisted of three parts: an acute in vivo test, a subchronic in vivo test, and an in vitro study. In the acute test, 0 to 200 mg/kg Propyl Gallate was administered orally to each of 10 mice. Positive and negative controls were used. Animals then received intraperitoneally 2 ml *S. typhimurium* strains TA1530 and G46, as well as 2 ml *S. cerevisiae* strain D3 indicator organisms. Animals were killed 3 h later; peritoneal fluid was removed, bacterial counts were made, and the number of mutants was recorded. In the subchronic test, each of 10 mice received orally 0 to 3500 mg/kg Propyl Gallate daily for 5 consecutive days. Within 30 min after the last treatment, animals were inoculated with indicator organisms and treated as above. In the in vitro study, 0 to 100 μg/ml Propyl Gallate was added to plates containing the indicator organisms. After incubation, the number of mutants was recorded.

Propyl Gallate induced no significant increases in mutant or recombinant frequencies with *S. typhimurium* or *S. cerevisiae* in these in vitro or in vivo host-mediated assays.

The cytogenetic assay also consisted of acute and subchronic in vivo tests and an in vitro study. In the acute test, groups of 15 rats were given 5 to 5000 mg/kg Propyl Gallate by gastric intubation. Four hours later, each animal received intraperitoneally 4 mg/kg colchicine in order to arrest bone marrow cells in C-mitosis. Five animals at each dose were killed at 6, 24, and 48 h. Bone marrow was removed, and the chromosome preparations were scored for abnormalities. Positive and negative controls were used. In the subchronic study, groups of five mice received 0 to 5000 mg/kg Propyl Gallate daily for 5 consecutive days. Animals were killed 6 hours following the last dosing and treated as above. In the in vitro study, 0.5 to 50 μg/ml Propyl Gallate were added to human embryonic lung cultures in anaphase. Positive and negative controls were used. Chromosomal damage was then scored.

Propyl Gallate induced no detectable significant aberrations in the bone marrow metaphase chromosomes of rats and induced no significant aberrations in the anaphase chromosomes of human tissue culture cells in vitro.

In a dominant lethal assay, groups of 10 male rats received orally 0 to 5000 mg/kg Propyl Gallate once (acute study) or daily for 5 consecutive days (subchronic study). Positive and negative controls were used. Following treatment, males were mated with two virgin females per week for 7 or 8 weeks. Pregnant dams were killed 14 days after separation from treated males; the uteri were examined for resorption sites, late fetal deaths, and total implantations.

No dose-response or time-trend patterns that would suggest a dominant lethal effect for Propyl Gallate were observed; Propyl Gallate was nonmutagenic under the study conditions (Litton Bionetics 1974).

Ishidate et al. (1978) used a chromosomal aberration assay to study the activity of Propyl Gallate. The test material was added to cultures of Chinese hamster fibroblast cells at concentrations up to 0.04 mg/ml in saline. Chromosome preparations were made 24 h later. Propyl Gallate induced chromosomal gaps, breaks, exchanges, and fragmentations in 20% of the cells at a concentration of 0.023 mg/ml. The authors found that this compound produced significant aberrations under these test conditions.

Sasaki et al. (1980) tested the cytogenetic activity of Propyl Gallate in a diploid human embryo fibroblast cell line. Propyl Gallate was added to cell cultures at concentrations of 0 to 0.0212 mg/ml for 26 to 48 h. Chromosome preparations were then made, and aberrations as well as sister chromatid exchanges were scored. At the highest dose tested, Propyl Gallate was toxic to cells. At the lower concentration (0.0021 mg/ml), Propyl Gallate did not induce significant chromosomal aberrations or sister chromatid exchanges.

In an Ames test, Simmon and Eckford (1978) tested Propyl Gallate for mutagenic activity in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, as well as *E. coli* strain WP2 at doses of 0.03 to 1000 μg/plate. Assays were performed in the presence and absence of Aroclor 1254–induced rat hepatic microsomes. Propyl Gallate was toxic to all strains at 333 and 1000 μg/plate. No significant mutagenicity was produced either with or without metabolic activation in all indicator organisms.

Rosin and Stich (1980), in another Ames test, added Propyl Gallate to cultures of *S. typhimurium* strains TA98 and TA100 at concentrations of 0.1 to 10 mM. Assays were performed in the presence and absence of Aroclor 1254–induced rat hepatic microsomes. Propyl Gallate was nontoxic to cells except at the highest test concentration and did not induce significant mutagenic frequencies both with and without activation when compared to solvent control values.

Shelef and Chin (1980) also used the Ames test to study the mutagenicity of Propyl Gallate. The test material was added to cultures of *S. typhimurium* TA98 and TA100 at doses of 0 to 50 μg/plate. Assays were performed in the presence and absence of Aroclor 1254–induced rat liver microsomes. Although Propyl Gallate was toxic to cells at the highest dose tested (50 μg/plate), it was not mutagenic with or without metabolic activation.

In a study by Kawachi et al. (1980), the Ames test (with TA100 and TA98), a rec-assay (with *Bacillus subtilis*), a chromosomal aberration/sister chromatid exchange assay (in hamster lung and human embryo fibroblasts), an in vivo chromosomal aberration test (in rat bone marrow), and a silkworm mutation assay were used to determine the mutagenicity of Propyl Gallate. No concentrations or doses were listed. In all assays, Propyl Gallate was assayed without metabolic activation. Propyl Gallate was mutagenic in the rec-assay and in the hamster lung chromosomal aberration assay. In all other test systems, Propyl Gallate was nonmutagenic.

Jacobi et al. (1998) reported that >0.25 μM Propyl Gallate with 5 μM copper (as $CuCl_2$) induced single strand breaks in PM2 DNA. The same concentrations of Propyl Gallate with 100 μM copper induced double-strand breaks. DNA strand breakage was prevented by the addition of catalase of the Cu(I) chelator neocuproine. Neither Propyl Gallate nor $CuCl_2$ alone caused any strand breaking. In human fibroblasts, 0.15 to 0.5 mM Propyl Gallate with 2.5 mM $CuCl_2$ induced DNA strand breaks. Cell viability, as measured by the MTT assay, was not reduced by more than 10%, but cell growth was inhibited. The authors proposed that Propyl Gallate interacts with copper by redox reactions, and reactive species are formed.

Chen and Chung (2000) reported that 125 to 1000 μg/plate Propyl Gallate was not mutagenic in *Salmonella* strains TA98 and TA100. Propyl Gallate (0.1 or 0.2 μmol) was also found not to be anti-mutagenic, as it did not protect TA98 or TA100 from known direct mutagens.

Tayama and Nakagawa (2001) reported that Propyl Gallate at 0.25 to 1.5 mM with S9 activation induced sister chromatid exchanges, chromosomal aberrations, and endoreduplications in Chinese hamster ovary (CHO-K1) cells, followed by delays in the cell cycle.

Mutagenesis Enhancement

Rosin and Stich (1980) reported that Propyl Gallate (0.1 to 10 mM) enhanced the mutagenic effect of *N*-hydroxy-2-acetylaminofluorine and 4-nitroquinoline-1-oxide (4-NQO) in *S. typhimurium* strains TA98 and TA100, respectively. Bacterial cultures were suspended in a mixture of Propyl Gallate, chemical to be tested, dimethyl sulfoxide, and saline. A 580% to 700% increase in mutation frequency was observed without metabolic activation only. Propyl Gallate also induced a 700% increase in the mutagenic frequency of 4-NQO in TA98 and was also toxic to cells (only 16% cell survival). Therefore, Propyl Gallate may enhance the reduction of 4-NQO to a mutagenic product.

Antimutagenesis

Propyl Gallate inhibited the mutagenic activity of dimethylnitrosamine in a DNA-repair test. They suggested that antioxidants may act as antimutagens by preventing the formation of reactive carcinogens or by competing with proximate carcinogens or mutagens (Lo and Stitch 1978).

In two studies, Propyl Gallate (25 to 125 μM and 410 nmol/plate) inhibited the mutagenic activity of benzo[*a*]pyrene (BP) metabolites in *S. typhimurium* strain TA98 (Rahimtula et al. 1977; Calle and Sullivan 1982).

Rahimtula et al. (1977) claimed that Propyl Gallate inhibited BP hydroxylase in the microsomal preparation.

Springarn and Garvie (1979) reported that Propyl Gallate inhibited the formation of mutagenic pyrazine derivatives in sugar-ammonia systems when assayed in *S. typhimurium* TA98 and TA100 in the presence and absence of rat hepatic microsomes. In another study, Propyl Gallate inhibited the mutagenicity of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine and *N*-acetoxy-2-acetyl-aminofluorine in the same test organisms (Rosin and Stitch 1979).

Propyl Gallate also reduced the mutagenic activity of pyrolysis products of albumin (0.2 g Propyl Gallate to 1 g albumin) in Ames assays using *S. typhimurium* TA98 (Fukuhara et al. 1981). In addition, Propyl Gallate reduced the mutagenic activity of aflatoxin B1 in *S. typhimurium* TA98 under metabolic activation (Rosin and Stitch 1980), but in a similar study, it slightly increased (by 50 to 100% at highest dose tested) the mutagenic effect of this carcinogen in *S. typhimurium* TA100 (Shelef and Chin 1980).

CARCINOGENICITY

Stoner et al. (1973) tested Propyl Gallate for its ability to induce pulmonary tumors in groups of 30 strain A mice. The test material was injected intraperitoneally at doses of 0.6 or 2.4 g/kg, three times weekly for 8 weeks (24 injections). Positive, negative, and vehicle controls were also included in the study. At 24 weeks, animals were killed, and the lungs were examined for tumor formation and other abnormalities. No significant differences were observed in the number of pulmonary tumors between test and control animals.

Propyl Gallate was tested for carcinogenicity in the National Toxicology Program (NTP 1982, also reported by Abdo et al. 1986) by feeding diets containing 6,000 or 12,000 ppm Propyl Gallate to 50 F344 rats and 50 B6C3F1 mice of each sex for 103 weeks. Control groups of 50 rats and mice of each sex were kept.

Tumors of the preputial gland, pancreatic islet cells, and adrenal gland (pheochromocytomas) were found in low-dose male rats at significantly higher levels than in controls. However, they were not increased in the high-dose males and were within the range of historical controls. Similarly, thyroid follicular cell tumors occurred in the dosed male rats but were not significant in comparison to untreated controls and comparable to historical controls. Rare brain tumors were found in two low-dose female rats; none were found in the high-dose group. Adenomas of the mammary gland also occurred in the high-dose female rats but were not significant compared to controls. Adenomas of the liver occurred in the high-dose female mice at a significantly higher level than in the concurrent controls, but this incidence was within the historical range for this tumor.

All of these tumors were considered unrelated to the administration of Propyl Gallate. The high-dose male mice had a significant increase in malignant lymphomas relative to concurrent controls but not statistically significant when compared with the historical rate.

Under the conditions of the bioassay, Propyl Gallate was not considered to be carcinogeneic for F344/N rats, although there was evidence of an increased proportion of low-dose male rats with preputial gland tumors, islet-cell tumors of the pancreas, and pheochromocytomas of the adrenal glands; rare tumors of the brain occurred in two low-dose females.

Propyl Gallate was not considered to be carcinogenic for B6C3F1 mice of either sex, although the increased incidence of malignant lymphomas in male mice may have been related to the dietary administration of Propyl Gallate (NTP 1982, also reported by Abdo et al. 1986).

Anticarcinogenesis/Antitumorigenesis

Emanuel et al. (1959) reported that Propyl Gallate inhibited the activity of important oxidation-reduction enzymes necessary for the intensive biosynthetic processes of tumor cells in vitro. Further, Propyl Gallate (0.01% to 0.75%) selectively reduced the RNA content of tumor cells without significantly affecting the RNA content of normal, noncancerous cells. Tumor cells treated with this ingredient also lost their implantability into host animals. Lipchina et al. (1960) observed that Propyl Gallate (0.15 mg/ml) suppressed mitosis in HeLa tumor cells; its selectivity for tumor cells was dependent upon concentration and time of exposure. Propyl Gallate also significantly increased the number of chromosome aberrations and altered the metabolic activity of tumor cells. These authors concluded that Propyl Gallate's selectivity may be due to a difference in the content of natural inhibitors between tumor and normal cells.

Kukushkina et al. (1966a, 1966b) reported that Propyl Gallate inhibited protein and nucleic acid biosynthesis in Erhlich ascites carcinomas and solid hepatomas, whereas in vivo it did not affect these biosynthetic processes in healthy tissue. Furthermore, Propyl Gallate inhibited these processes in cultured human laryngeal cancer cells. Emanuel et al. (1976) reported that Propyl Gallate inhibited RNA formation in Ehrlich ascites carcinoma cell preparations. The addition of 10 and 40 μg/ml Propyl Gallate to the incubation mixture caused inhibition of the synthesis of the RNA product by 55% and 80%, respectively. This effect was thought to be due to the interaction of Propyl Gallate with the SH groups of enzymes involved with RNA transcription.

McCay et al. (1981) observed that Propyl Gallate protected rats against the induction of tumors by dimethylbenzanthracene (DMBA). Six groups of 30 weanling rats were placed on diets containing polyunsaturated fat, saturated fat, or no fat, with or without addition of 0.3% Propyl Gallate. Fifty days later, half of each group were given 10 mg DMBA orally. Six months later, all rats were killed and examined for tumors. The results indicated that Propyl Gallate inhibited DMBA-induced tumorigenesis; however, both the amount of fat and degree of unsaturation affected the extent of inhibition.

Kozumbo et al. (1982) investigated the role of reactive oxygen species in tumor promotion by examining the effects of antioxidants on the 12-*O*-tetradecanoyl phorbol-13-acetate (TPA)-induced ornithine decarboxylase (ODC) activity. Propyl Gallate (50 μmol) applied topically to mouse epidermis substantially inhibited TPA-induced ODC activity. Propyl Gallate may inhibit the promotion phase of carcinogenesis.

Radiation Coeffects

Aphanasjev et al. (1968) first reported the radio-sensitizing effect of Propyl Gallate on tumors. Multiple intraperitoneal injections of this ingredient enhanced the lethal action of local ionizing radiation for lymphosarcomas in mice. More Propyl Gallate–treated mice had regressing tumors than those receiving radiation alone; additionally, the growth of nonregressing tumors decreased in these test animals.

Odintsova and Kruglyakova (1976), in experiments with isolated DNA, reported that the radioprotective effect of Propyl Gallate increased as the concentration of unoxidized Propyl Gallate (maximum effect at 1.65×10^{-2} M) increased before radiation and likewise the radioprotective effect decreased as the time of preirradiation exposure to unoxidized and oxidized Propyl Gallate increased. This latter decrease in the radioprotective effect can, in some cases, result in radiosensitization; initial injury to DNA by Propyl Gallate before radiation enhances the injurious effects of radiation.

Inhibition of Nitrosamine Formation

Kawanishi et al. (1981) found that Propyl Gallate inhibited nitrosamine formation from aminopyrine and sodium nitrite in rat stomachs. Inhibition was as high as 55% at a dose of 100 μmol Propyl Gallate per kg body weight; Propyl Gallate was considered a relatively strong inhibitor. Similarly, Rao et al. (1982) observed that Propyl Gallate inhibited nitrosamine formation in human saliva from the interaction of salivary nitrite with aminopyrine and oxytetracycline by acting as a nitrite scavenger. Inhibition produced by 10 mM Propyl Gallate ranged from 42% to 53% at pH 3.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Telford et al. (1962) studied the effect of Propyl Gallate in nine female rats and their offspring. Animals were mated and then given a total dosage of 0.5 g per rat in the diet. On the 22nd day of gestation, the rats were killed, and the young were removed for study. At the dose tested, Propyl Gallate was nontoxic to the pregnant rats, although it substantially increased fetal resorption rates (18.3% resorption; 77.7% litters with resorptions) when compared to controls (10.6% resorption; 40.8% litters with resorptions).

Daniialov (1966) delivered a 2:1 mixture of butylhydroxyanisole and Propyl Gallate in chronic tests carried out on male and female white rats (type unspecified). The test was performed on three groups of male and three groups of females with 10 animals each. Five were used in the first round and five in the second round. The animals in the first and fourth groups were administered the antioxidants (butylhydroxyanisole and Propyl Gallate) at 100 times (butylhydroxyanisole 20 mg/kg, Propyl Gallate 10 mg/kg) the amount which can enter a human body. Animals of the second and fifth groups were administered a mixture of antioxidants at 10 times the amount (butylhydroxyanisole 2 mg/kg,

Propyl Gallate 1 mg/kg). The third and sixth groups were used as the controls. The antioxidants were administered in rendered pig fat as feed pellets. In the sixth month, the animals of the two groups were mated to obtain a second generation. Rats that were fed antioxidants were unable to reproduce. Of the five animals in group 4, none reproduced. Of the five females of group 5, only one had offspring, whereas among the control females, three had offspring.

To confirm these results, the experiment was repeated on the other animals. In the second round, of the five rats that received the mixture of antioxidants at 100 times exaggeration, none reproduced. Of the five animals administered at 10 times exaggeration, only one had a litter. Among the control animals, four had young. It was concluded that the administration of butylhydroxyanisole and Propyl Gallate to white rats causes sterility (Daniialov 1966).

Food and Drugs Research Labs (FDRL) (1972b) studied the effects of Propyl Gallate on pregnant rats, mice, and hamsters. Twelve groups of 22 to 25 pregnant animals were given orally 3.0 to 300 mg/kg (rats, mice) or 2.5 to 250 mg/kg (hamsters) Propyl Gallate. Doses were given daily from days 6 to 10 (hamsters) or day 15 of gestation (rats, mice). Positive (aspirin) and negative (corn oil) controls were used. Animals were observed for signs of toxicity, and body weights were monitored. On gestation day 14 (hamsters), 17 (mice), or 20 (rats), all dams were killed and the fetuses removed. Numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. Urogenital tracts of females were examined for abnormalities. All fetuses were examined for visceral, skeletal, and external abnormalities.

Oral administration of up to 250 mg/kg Propyl Gallate for 5 consecutive days in hamsters or up to 300 mg/kg Propyl Gallate for 10 consecutive days in rats and mice had no effect on nidation or on maternal or fetal survival. The number of visceral, skeletal, and external abnormalities observed in the test group fetuses did not differ significantly from that of negative control groups (FDRL 1972b).

A similar study was performed on four groups of 20 to 50 pregnant rabbits given orally 2.5 to 250 mg/kg Propyl Gallate daily from days 6 to 18 of gestation. Positive (6-aminonicotinamide) and negative (corn oil) controls were used. Ingestion of up to 250 mg/kg Propyl Gallate for 13 consecutive days during gestation had no effect on nidation or maternal or fetal survival. The number of visceral, skeletal, and external abnormalities observed in the test group fetuses did not differ significantly from negative control groups (FDRL 1973).

Desesso (1981) studied the effects of Propyl Gallate on pregnant rabbits. Each rabbit received a subcutaneous injection of 634 mg/kg Propyl Gallate in a water-ethanol vehicle on the 12th gestational day. Two control groups were kept, one receiving the vehicle and the other remaining untreated. On the 29th day, the rabbits were killed and examined for resorptions and fetuses. No malformations and a low incidence of resorption were found in the six litters obtained from Propyl Gallate–treated rabbits. Weights of the fetuses in the Propyl Gallate group were significantly higher than those of the negative controls; however, they were similar to those of the vehicle controls.

Tanaka et al. (1979) reported a study in which groups of 18 to 20 pregnant Wistar rats were fed diets containing 0%, 0.4% (0.35 g/kg), 1% (0.88 g/kg), or 2.5% (2.04 g/kg) Propyl Gallate starting on day 1 of gestation. On the 20th day of gestation, 13 of 18 rats of the 2.5% group and 15 of 20 rats of the other groups were killed for fetal examination. Implantation sites and numbers of live and dead fetuses were counted; examinations of fetuses for organ and skeletal anomalies were then performed. The remaining dams from each group were allowed to give birth. Offspring were observed for 8 weeks, then killed, and tissues were examined microscopically for visceral and skeletal abnormalities.

At the highest concentration tested, maternal body weight and feed consumption were significantly lower than those of controls. However, no other signs of toxicity were observed in these rats. Body weight of fetuses at the highest concentration of Propyl Gallate was reduced but not significantly so. There was no difference in fetal mortality between control and test rats. Additionally, no significant incidence of external or internal organ abnormalities occurred in test fetuses. Although skeletal abnormalities were observed in some of the fetuses of Propyl Gallate–treated rats, they were considered to be spontaneous.

According to the authors, the only possible compound-related finding was a significant number of fetuses obtained from the 2.5% group with an insufficient number of caudal vertebrae. The only significant postnatal effect produced by Propyl Gallate was decreased viability in the 1% and 2.5% dose groups; this was due to cannibalism of the newborn by the dams. No behavioral or morphological changes were observed in the newborns from test mothers. Propyl Gallate was nonteratogenic (Tanaka et al. 1979).

Inhibition of Developmental and Reproductive Toxicity

King (1964) reported on Propyl Gallate–induced inhibition of teratogenesis induced by certain chemicals. When fed to vitamin E–deficient pregnant rats, Propyl Gallate prevented the teratogenic effects of the vitamin deficiency, as the incidence of congenital abnormalities and resorptions was reduced. Propyl Gallate was added to the diet at concentrations of 0% to 0.4% along with doses of 0 to 10 mg/rat vitamin E. On the 21st day of gestation, the rats were killed and the fetuses were examined. At 0.025%, Propyl Gallate did not reduce the frequency of vitamin E deficiency-induced malformations; at 0.4% alone or at lower concentrations with vitamin E supplements, Propyl Gallate reduced the teratogenic effects.

Desesso (1981) studied the effect of Propyl Gallate on hydroxyurea (HU)-induced teratogenesis. Various amounts of Propyl Gallate (362 to 906 mg/kg) and HU were injected simultaneously into rabbits or administered as a mixed solution on the twelfth gestational day. The highest dose of Propyl Gallate (906 mg/kg) was toxic to the pregnant animals, although increasing amounts of Propyl Gallate inhibited the effects of HU in a

dose-response relationship. Propyl Gallate reduced the number of malformed fetuses and resorptions, the severity of anomalies, and the range of HU-induced defects. The mixed solution of Propyl Gallate and HU was more efficacious than simultaneous injection of the compounds. However, data obtained by thin-layer chromatography indicated that the two compounds do not react chemically. The length of time the mixed solution was allowed to stand prior to injection also had no effect on the results. Desesso suggested that the antioxidant properties of Propyl Gallate acted within the embryo to reduce the severity of HU teratogenesis.

CLINICAL ASSESSMENT OF SAFETY

Irritation and Sensitization

Table 7 presents a summary of clinical dermal irritation and sensitization studies of Propyl Gallate and cosmetic formulations containing Propyl Gallate.

Propyl Gallate, as a 10% solution in propylene glycol, was applied to the skin of the back of the hand of each of two subjects for 24 h. No skin irritation was observed (Boehm and Williams 1943).

Lehman et al. (1951) reported a study in which Propyl Gallate (20% in alcohol) was applied to the forearms of 10 white subjects daily for about 24 days. Sites were examined twice weekly. For the first 14 days, there were no signs or complaints of irritation. During the last 10 days, 5 of the 10 subjects complained of pruritis and erythema. Three of these reactions were mild and subsided within a few days. The other two subjects developed a skin eruption that progressed up the arm and onto the trunk; the reaction required 3 weeks to heal. The investigators then applied single 48-hour patches containing 2% Propyl Gallate to two of the mildly sensitized reactors and to 25 nonsensitive control subjects. Both sensitized subjects reacted mildly to the patch, whereas none of the control subjects reacted to Propyl Gallate. Although Propyl Gallate was a contact sensitizer at high concentrations (10%), the authors suggested that human tolerance to low Propyl Gallate concentrations may be the result of repeated oral exposures to low doses of Propyl Gallate in food.

CTFA (1980e) reported the results of a repeat-insult patch test (RIPT) on a total of 16 subjects, using a lipstick formulation containing less than 1% Propyl Gallate. The test material, "sufficient to cover a Webril pad", was applied at 48- and/or 72-h intervals to the upper arms and covered for the first 24 h between applications. Each site was scored at 48 and/or 72 h when new patches were applied. The 22-day induction period was followed by a 12-day rest period before application of a 24-h occlusive challenge patch. No irritation was observed in the 15 subjects who completed the test program, but one subject had a mild sensitization reaction following the challenge application at an adjacent site. The test report stated that the score did not suggest "significant dermatotoxicity." It is unknown whether the volunteers for this study were free from skin diseases (CTFA 1980e).

Hill Top Research (1978) tested two lipstick formulations, each containing 0.005% Propyl Gallate, for cumulative irritancy using 14 subjects (12 completed the test). All subjects were free from any known skin conditions or allergies. Approximately 0.2 g of each lipstick and 0.3 ml of two reference materials (of low and high irritancy) were applied daily by occlusive patch to the back of each panelist. Patches were removed after 23 h and scored 1 h later, and the procedure was repeated for 21 consecutive days. The total calculated scores of the two formulations (based on 10 subjects) were 1.67 and 29.51, respectively, placing them in the "essentially nonirritating" classification (score of 0 to 49 on a maximum scale of 630). The total calculated scores for the low and high irritancy reference materials were 2.50 and 616.67, respectively.

Three suntan preparations, an oil, a cream, and a sun protection stick, were evaluated for irritation and sensitization by a modified Draize-Shelanski repeat-insult patch test (CTFA 1980f, 1977f; FDRL 1981). Each preparation contained 0.003% Propyl Gallate. Topical, occlusive patches were applied to the upper backs of the panelists on Monday, Wednesday, and Friday for 3 consecutive weeks. All panelists were free from any known skin conditions or allergies. Sites were scored (scale of 0 to 4) prior to each patch application. This induction phase was followed by a 2-week nontreatment period. Two consecutive 48-h challenge patches were then applied to adjacent sites and scored at 48 and 96 h. The suntan oil, tested on 151 subjects, produced eight scores of 1 and two scores of 2 on induction and no positive reactions on challenge. The suntan cream and sun protection stick produced no reactions when tested on 150 and 154 subjects, respectively. The investigators in all three studies observed no instances of sensitization.

Photosensitivity/Phototoxicity

Table 8 summarizes available photosensitivity/phototoxicity studies of Propyl Gallate and cosmetic formulations containing Propyl Gallate. At 10% in alcohol, Propyl Gallate was nonphotosensitizing to human skin. Cosmetic formulations containing 0.003% Propyl Gallate were essentially nonphotosensitizing and nonphototoxic.

Propyl Gallate, 10% in alcohol, was applied to the arms of 25 white subjects. Sites were dried, exposed to an FS-40 Westinghouse sunlamp (280 to 370 nm) at a dose of three times the individual's minimal erythemal dose (MED), and evaluated at 24 h. Propyl Gallate was then reapplied to the same site, allowed to dry, rinsed with warm water for 5 min, and radiated. Sites were evaluated at 24 h. No contact sensitization, photosensitization, or primary irritation was observed (Kahn and Curry 1974).

The photocontact sensitization of a sun protection stick containing 0.003% Propyl Gallate was evaluated in 25 subjects. A 0.2 ml sample of the sun stick was applied to the stripped skin of the back (one 2-inch square) of each subject. Sites were then exposed to three MEDs of xenon solar-simulating radiation and subsequently occluded. This procedure was repeated every

TABLE 7
Clinical irritation and sensitization studies with Propyl Gallate (PG)

Concentration tested	Type of test	No. tested	Findings	Reference
10% in proplyene glycol	Irritation—Applied to skin on back of hands for 24 h	2	No skin irritation	Boehm and Williams 1943
20% in alcohol	Irritation/sensitization—Applied to forearms daily for 24 days	10	3 exhibited mild reactions; 2 developed skin eruptions	Kahn et al. 1974
0.003% in a suntan butter	RIPT	150	No reactions; no instance of sensitization	CTFA 1977f
0.003% in a sun protection stick	RIPT	154	No reactions; no instance of sensitization	CTFA 1977g
0.005% in a lipstick	Cumulative irritancy	12	Score of 1.67 (max. = 630); essentially nonirritating	Hill Top Research 1978
0.005% in a lipstick	Cumulative irritancy	12	Score of 29.51 (max. = 630); essentially nonirritating	Hill Top Research 1978
<1% in a lipstick	RIPT[a]	15	No irritation; 1 mild sensitization on challenge; did "not suggest significant dermatoxicity"	CTFA 1980e
0.003% in a suntan oil	RIPT	151	8 scores of 1 (max. = 4) and 2 scores of 2 on inductions; no reactions on challenge; no significant allergic reactions	CTFA 1980f
0.003% in a sunscreen	RIPT	52	Slight transient reactions; no irritation or sensitization	FDRL 1981a
0.003% in a sunscreen	RIPT	52	Slight transient reactions; no irritation or sensitization	FDRL 1981b
0.003% in a sunscreen	RIPT	54	Slight transient reactions; no irritation or sensitization	FDRL 1981c
0.003% in a sunscreen	RIPT	54	Slight transient reactions; no irritation or sensitization	FDRL 1981d
0.003% in a sunscreen	RIPT	54	Slight transient reactions; no irritation or sensitization	FDRL 1981e
0.003% in a cosmetic formulation	RIPT	54	Slight transient reactions but for a score of 2 (max. = 4) on 2nd induction patch; no subsequent reactions observed; no irritation or sensitization	FDRL 1981f
0.003% in a cosmetic formulation	RIPT	54	Slight transient reactions; no irritation or sensitization	FDRL 1981g
1%, 0.1%, 0.05%, and 0.01% in petrolatum	Patch tests	1	Allergenic contact sensitivity to PG	Bojs et al. 1987
1% in ethanol and 0.1% in petrolatum	Patch tests	1	Positive reaction to PG	Cusano et al. 1987
0.5% in acetone	Patch tests	5	Contact dermatitis	Fiss and Wagner 1988

TABLE 7
Clinical irritation and sensitization studies with Propyl Gallate (PG) *(Continued)*

Concentration tested	Type of test	No. tested	Findings	Reference
1% in pet.	Patch tests	2	Positive reactions to PG	Valsecchi and Cainelli 1988
1% in pet.	Patch tests	6	Positive reactions to PG	Heine 1988
2% in pet.	Patch tests	1	Positive reaction to PG	Wilson et al. 1989
dissolved in ethanol:water (25:75)	Occluded patch test	5	Thresholds for positive reactions were 0.0025% for upper arm occluded patch; 0.0035% for underarm without shaving, 0.005% for underarm without shaving, and 0.015% for antecubital fossa	Kraus et al. 1990
1% in petrolatum	Patch tests	10	Positive allergic reactions to PG	Marston 1992
1% in petrolatum	Patch tests	1	Positive reaction to PG	Wilkinson and Beck 1992
1% in petrolatum	Patch tests	1	Positive reaction to PG and octyl gallate (0.25% in petrolatum)	Athavale and Srinivas 1994
0.5%, 1%, and 2% in petrolatum	Patch tests	1	Positive reaction to PG	Corazza et al. 1994
Various gallates (methyl, ethyl, propyl, octyl) in 0.3% and 0.1% w/w	Patch tests	1	Positive reactions to all except possibly methyl gallate at day 2 at 0.3% and ethyl gallate at day 2 (0.1%)	Hemmer 1996
Not specified	Patch tests	1	Positive reaction to PG	Hernández et al. 1997
1% in pet.	Patch tests	1	Positive reaction to PG	Mahendran et al. 2002
Saturated in ethanol	Patch tests	1	Positive reaction to PG	Mahendran et al. 2002

[a]RIPT, repeat-insult patch test.

48 h for five applications. After a 10-day rest, subjects were challenged on both normal and stripped skin in the same manner; however, this time the radiation was filtered through window glass. Sites were again occluded and evaluated at 24, 48, and 72 h. No reactions were observed. The sun protection stick was not a photosensitizer under the test conditions (CTFA 1977h).

Seven cosmetic formulations, including five sunscreens, were tested for photosensitization in 26 to 28 subjects. Each formulation contained 0.003% Propyl Gallate. Occlusive patches containing 0.2 g of each product were applied to the volar arms of the subjects for 24 h. Patches were then removed and sites were scored for irritation (scale of 0 to 4). One forearm of each subject was irradiated with four GE F40 BL lamps for 15 min, resulting in a total UVA dosage of 4400 μW/cm^2; the other forearm served as the nonradiated control. This procedure was repeated three times per week for 10 applications/radiations. After an 11- to 20-day rest, adjacent sites were challenged with a 24-h patch application followed by radiation. These sites were scored 24 and 48 h later. Six of the formulations produced only slight transient erythemal reactions (scores of $\pm$, 1); the seventh also produced slight reactions except for a score of 2 (erythema and edema) on the second induction patch. No subsequent reactions were observed. These formulations did not produce photosensitization in humans (FDRL 1981a, 1981b, 1981c, 1981d, 1981e, 1981f, 1981g).

Each of these seven formulations was also tested for phototoxicity in 10 subjects. Occlusive patches containing 0.2 g samples of each product were applied to the scrubbed, tape-stripped volar arms for 24 h. Sites were scored on patch removal, and one arm of each subject was then irradiated with UVA light for 15 min for a total dose of 4400 μW/cm^2. Sites were scored again immediately following, 24 and 72 h, and 7 days after radiation. Four of the formulations produced no reactions; the other three produced only slight transient reactions. No phototoxicity was produced by these formulations (FDRL 1981a, 1981b, 1981c, 1981d, 1981e, 1981f, 1981g).

TABLE 8
Clinical photosensitivity/phototoxicity of Propyl Gallate

Concentration tested	Type of test	No. tested	Findings	Reference
10% in alcohol	Photosensitization	25	No contact sensitization or primary irritation observed; effective compound for protection against UV light–induced erythema	Kahn and Curry 1974
0.003% in a sun protection stick	Photocontact sensitization	25	No reactions; not a photosensitizer under test conditions	CTFA 1977h
0.003% in a sunscreen	UVA Photosensitization	26	Slight transient reactions; no photosensitization	FDRL 1981a
0.003% in a sunscreen	UVA Photosensitization	26	Slight transient reactions; no photosensitization	FDRL 1981b
0.003% in a sunscreen	UVA Photosensitization	28	Slight transient reactions; no photosensitization	FDRL 1981c
0.003% in a sunscreen	UVA Photosensitization	28	Slight transient reactions; no photosensitization	FDRL 1981d
0.003% in a sunscreen	UVA Photosensitization	28	Slight transient reactions; no photosensitization	FDRL 1981e
0.003% in a cosmetic formulation	UVA Photosensitization	26	Slight transient reactions; no photosensitization	FDRL 1981g
0.003% in a cosmetic formulation	UVA Photosensitization	26	Slight transient reactions but for a score of 2 (max. = 4) on 2nd induction patch; no subsequent reactions observed; no photosensitization	FDRL 1981f
0.003% in a sunscreen	UVA Phototoxicity	10	Slight transient reactions; no phototoxicity	FDRL 1981a
0.003% in a sunscreen	UVA Phototoxicity	10	Slight transient reactions; no phototoxicity	FDRL 1981b
0.003% in a sunscreen	UVA Phototoxicity	10	No reactions; no phototoxicity	FDRL 1981c
0.003% in a sunscreen	UVA Phototoxicity	10	No reactions; no phototoxicity	FDRL 1981d
0.003% in a sunscreen	UVA Phototoxicity	10	No reactions; no phototoxicity	FDRL 1981e
0.003% in a cosmetic formulation	UVA Phototoxicity	10	Slight transient reactions; no phototoxicity	FDRL 1981f
0.003% in a cosmetic formulation	UVA Phototoxicity	10	No reactions; no phototoxicity	FDRL 1981g
0.003% in a sun protection stick	UVA Phototoxicity	10	No reactions; not phototoxic under test conditions	CTFA 1977i
0.003% in a suntan oil	Controlled use	78	No clinically significant reactions observed; safe for intended use	CTFA 1980g

The phototoxicity of a sun protection stick containing 0.003% Propyl Gallate was evaluated using 10 subjects. Applications of 5 ml/cm^2 of the sun stick were rubbed into the lower back of each subject and then occluded for 24 h.

Patches were removed, and the sites were radiated for 20 min with filtered long-wave UV light (UVA 30 mW/cm^2) using a 150 W xenon solar simulator (emission of 124 mW/cm^2). Adjacent skin sites received similar treatment as controls. Reactions were graded 24 and 48 h later. No reactions were observed; the investigators concluded that the sun protection stick was not phototoxic under the test conditions (CTFA 1977i).

A suntan oil containing 0.003% Propyl Gallate was evaluated by a 2-day controlled use test. Each of the 78 subjects applied the oil to exposed parts of the body at 30-min intervals for 2 h of continuous sun exposure (11:30 am to 1:30 pm). Subjects were required to enter the pool for 10 min at the end of each hour. These procedures were repeated the second day. Any reactions immediately, 24 h, or 48 h after application were noted. No clinically significant reactions were observed; the product was considered safe for intended use (CTFA 1980g).

Case Reports

Boehm and Williams (1943) reported the case of a man who ingested 0.5 g Propyl Gallate daily for 6 consecutive days. Urine was collected during this time and for 6 days after the final administration. The urine was negative for albumin, abnormal sedimental contents, red blood cells, and casts. The authors concluded that Propyl Gallate was safe and effective as an antioxidant in medicinal and pharmaceutical preparations.

Nitzan et al. (1979) reported nine infants in a pediatric ward of a hospital found to have significant methemoglobinemia. A fat preservative in an infant formula was considered the probable source of toxicity. When the preservative was removed from these infants' diet, methemoglobin concentrations returned to normal within 48 to 96 h. The preservative was identified as a mixture of BHA, BHT, and Propyl Gallate. In addition, age was an important factor with respect to the toxicity of phenolic compounds, because only newborn babies (6 to 15 weeks old) and not older babies were affected by the preservative in the formula. Pyrogallol, which is chemically related to Propyl Gallate, had been previously implicated in methemoglobinemia.

Bojs et al. (1987) published a case report of a 60-year-old woman who developed eczema on the hands, forearms, face, neck, legs, and buttocks after using a Swedish-made moisturizing cream, "Idomin Fukt." Patch tests of each of the ingredients produced reactions only to Propyl Gallate at 1%, 0.1%, 0.05%, and 0.01% in petrolatum.

Cusano et al. (1987) reported that a 68-year-old woman developed severe eczematous dermatitis on her right leg after applying Dermoangiopan gel for 2 weeks. Patch tests of the gel and each of its ingredients revealed positive results for sensitivity to the gel and to 1% Propyl Gallate in ethanol.

Fiss and Wagner (1988) described five patients, four females and one male, who each developed irritation on their face, hands, and bodies after using Elasan Babylotion. All of the patients had positive epicutaneous tests with 0.5% Propyl Gallate in acetone.

Valsecchi and Cainelli (1988) described a 21-year-old man and a 34-year-old woman who each developed severe irritation after applying an antibiotic ointment, Traumatociclina. Patch tests of the ointment and each ingredient showed sensitivity reactions to the ointment and to 1% Propyl Gallate in petrolatum.

Heine (1988) reported that six female patients exhibited contact dermatitis after using a "lotion for care of the body and babies," which contained Propyl Gallate. All of the patients tested positive for sensitivity to the lotion and to 1% Propyl Gallate in petrolatum. The dermatitis cleared after discontinuing use of the lotion.

Wilson et al. (1989) described a 58-year-old woman who developed florid cheilitis after chronic use of a lip balm for 7 years to prevent chapping. Of the ingredients patch-tested, 2% Propyl Gallate (in petrolatum) gave positive reactions.

Kraus et al. (1990) studied the dose response of allergic contact dermatitis from Propyl Gallate in five Propyl Gallate-sensitive human subjects. Using Propyl Gallate dissolved in ethanol:water (25:75), the thresholds for positive reactions were as follows: 0.0025% for the upper arm occluded patch; 0.0035% for the underarm without shaving; 0.005% for the underarm with shaving; and 0.015% for the antecubital fossa.

Marston (1992) described 10 case reports in which users of various creams and cosmetics had positive reactions to 1% Propyl Gallate in petrolatum.

Wilkinson and Beck (1992) described a 35-year-old man who had acute swelling and erythema after using Timodine cream that contained Propyl Gallate. There was a positive reaction to 1% Propyl Gallate in petrolatum, but not to any of the other ingredients.

Athavale and Srinivas (1994) described a case in which a 23-year-old woman had scaling and swelling of her lips after using a certain lipstick. She was patch tested with the ingredients, and had positive reactions to 1% Propyl Gallate in petrolatum and 0.25% Octyl Gallate in petrolatum.

As described by Corazza et al. (1994), a 42-year-old woman had acute eczema after using ointments to treat a burn injury. One of the ointments was traumatocycline, which contained 8% Propyl Gallate. The ingredients of this cream were patch tested, and only Propyl Gallate at 0.5%, 1%, and 2% in petrolatum was positive.

Hemmer et al. (1996) reported that a 54-year-old woman who had sensitivity reactions to 1% Propyl Gallate in a cosmetic preparation was also sensitive to tri- and *ortho*-diphenols (catechols).

Hernández et al. (1997) reported a case of a 59-year-old man who developed erythema and edema after using Locapred cream. Of the ingredients patch-tested, only Propyl Gallate was positive (positive dose not specified).

Mahendran et al. (2002) described a 41-year-old man who had erythema and edema around the eyes. He worked in textile manufacturing and used Propyl Gallate as a stabilizing agent. He was routinely exposed to Propyl Gallate in powder form. Patch tests revealed that he had positive reactions to 1% Propyl Gallate in petrolatum and to saturated Propyl Gallate in ethanol.

SUMMARY

Propyl Gallate is the n-propyl ester of gallic acid (3,4,5-trihydroxybenzoic acid). It is soluble in ethanol, ethyl ether, oil, lard, and aqueous solutions of PEG ethers of cetyl alcohol (ceteths) but only slightly soluble in water. Propyl Gallate is an antioxidant that reacts chemically to inhibit the generation or accumulation of free radicals in chemical and biological systems. It is stable in neutral or slightly acidic solutions but loses stability in mild alkaline environments or when heated.

In cosmetics, Propyl Gallate is used as an antioxidant to stabilize vitamins, essential oils, perfumes, fats and oils. Although it may be used alone, it is generally used in combination with other antioxidants. Propyl Gallate was reported to be used in 167 cosmetic products at maximum concentrations of 0.1%. Propyl Gallate is a generally recognized as safe (GRAS) antioxidant to protect fats, oils, and fat-containing food from rancidity that results from the formation of peroxides.

Propyl Gallate is absorbed when ingested, then methylated, conjugated, and excreted in the urine. Other urinary metabolites included pyrogallol (free and conjugated) and gallic acid.

Propyl Gallate has numerous biological effects, most as a direct result of this ingredient's free-radical scavenging ability. Biological effects include antimicrobial activity, enzyme inhibition, inhibition of biosynthetic processes, inhibition of the formation of nitrosamines, anesthesia, inhibition of neuromuscular response to chemicals, ionizing/UV radiation protection, chemoprotection, antimutagenesis, anticarcinogenesis and antitumorigenesis, antiteratogenesis, and anticariogenesis.

Acute animal toxicity studies indicate that Propyl Gallate was slightly toxic when ingested. No systemic toxic effects were noted when Propyl Gallate was applied to the skin. Findings in subchronic studies include: 20% Propyl Gallate induces reversible epidermal changes when applied to the skin of guinea pigs for 6 weeks; this ingredient does not induce depigmentation when applied to the skin of black guinea pigs for 1 to 6 months; and Propyl Gallate is practically nontoxic or slightly toxic when ingested at concentrations up to 0.5% or doses up to 500 mg/kg. Propyl Gallate was a strong sensitizer when tested intradermally, less sensitizing when tested topically, and nonsensitizing topically at 0.1% in one study. In a second study, Propyl Gallate (15 mg dissolved in 8 ml vehicle) was sensitizing to guinea pigs. In a local lymph node assay, 5% Propyl Gallate was sensitizing to mice. Acute eye irritation tests conducted on nine cosmetic formulations, each containing less than 1% Propyl Gallate, were negative. A phototoxicity study conducted on a cosmetic formulation containing 0.003% Propyl Gallate determined that the product was not phototoxic to guinea pigs.

Numerous chronic oral toxicity studies indicate that Propyl Gallate, when ingested at concentrations up to 5% in the diet for up to 2 years, was practically nontoxic to rats, mice, dogs, and guinea pigs. Repeated oral ingestion of 0.5 g Propyl Gallate did not result in toxicity in rats and pigs.

Five Ames studies were negative; however, chromosomal aberration assays, sister-chromatid exchange assays, cytogenetic assays, dominant lethal assays, host-mediated assays, and a silkworm mutation assay results were mixed.

Propyl Gallate was nontumorigenic when injected intraperitoneally in strain A mice at doses up to 2.4 g/kg 3 times weekly for 8 weeks. The National Toxicology Program reported that Propyl Gallate was noncarcinogenic in mice and rats.

Female rats fed 0.5 g Propyl Gallate had substantially increased fetal resorption rates when compared to controls. However, in four separate teratogenesis studies, Propyl Gallate at doses up to 2.04 g/kg was nonteratogenic in rats, rabbits, mice, or hamsters.

In clinical cumulative irritancy tests, Propyl Gallate was nonirritating at concentrations up to 10%. Patch tests at concentrations less than 1% yielded positive elicitation responses. RIPTs conducted on cosmetic formulations containing 0.003% Propyl Gallate produced no irritation or sensitization. Propyl Gallate at a concentration of 10% in alcohol was nonphototoxic in 25 subjects. Cosmetic formulations, each containing 0.003% Propyl Gallate, produced no signs of photosensitization or phototoxicity in a total of 371 subjects.

DISCUSSION

Little systemic toxicity is associated with oral or dermal exposure to Propyl Gallate, and the high octanol:water partition coefficient suggests little dermal penetration. Most effects that are reported relate to the ability of Propyl Gallate to scavenge free radicals, including ionizing/UV radiation protection, anticarcinogenesis, antiteratogenesis, and anticariogenesis.

Although Propyl Gallate is not a skin irritant in clinical tests, it may induce skin sensitization. Additional data, available since the initial safety assessment was completed in the mid-1980s, suggest that sensitization may be possible at lower concentrations of Propyl Gallate than originally thought, i.e., at concentrations less than 1%. The Panel noted that there are limited animal tests on which to base an acceptable concentration, and these RIPT tests were conducted using extremely low concentrations and not particularly useful in establishing a safe level.

In actual practice, cosmetic formulations contain Propyl Gallate at concentrations up to 0.1%. The Panel noted that the number of formulations containing Propyl Gallate has increased since the original safety assessment was done. In spite of the increased exposure associated with increased use, it is the clinical experience of the Panel that the use of Propyl Gallate in cosmetics has not resulted in sensitization reactions. Therefore,

the Panel believes that a concentration limitation of 0.1% in cosmetics is necessary (given the evidence of sensitization at concentrations less than 1%) and sufficient (given that current products are not producing adverse reactions).

CONCLUSION

On the basis of the data presented in this report, the CIR Expert Panel concludes that Propyl Gallate is safe in the practices of use as described in this safety assessment at concentrations less than or equal to 0.1%.

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