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## Final Report on the Safety Assessment of Propyl Gallate

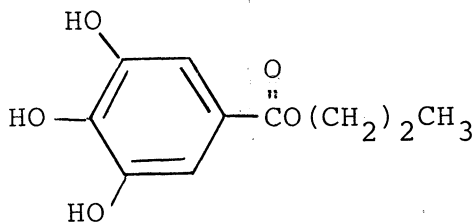
Propyl Gallate acid is used as an antioxidant in cosmetic products at concentrations normally less than 0.1 percent. Propyl Gallate is absorbed when ingested, methylated, conjugated, and excreted in the urine. Acute animal toxicity studies indicate that Propyl Gallate is slightly toxic when ingested and practically nontoxic when applied to the skin. Numerous chronic oral toxicity studies indicate that Propyl Gallate at concentrations up to 5 percent is practically nontoxic to rats, mice, dogs, and guinea pigs.

Propyl Gallate is nonirritating to human skin at concentrations up to 10 percent; however, it is sensitizing at this and higher concentrations. Propyl Gallate was nonphototoxic. It is concluded that Propyl Gallate is safe as a cosmetic ingredient at concentrations not exceeding 1 percent.

### CHEMISTRY

#### Description and Preparation

**P**ropyl Gallate is the *n*-propyl ester of gallic acid. It conforms to the following structure<sup>(1)</sup>:



Other names for this ingredient include<sup>(2)</sup>:

3,4,5-Trihydroxybenzoic acid propyl ester  
*n*-Propyl gallate  
Gallic acid propyl ester

PG  
Progallin P  
Tenox PG

Propyl Gallate is produced commercially by the esterification of gallic acid (trihydroxybenzoic acid) with propyl alcohol.<sup>(3)</sup>

### Properties

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.<sup>(2,4,5)</sup> Propyl Gallate is also soluble in aqueous solutions of PEG ethers of cetyl alcohol; solubility increases as the concentration of the surfactant increases and the PEG chain length increases.<sup>(6)</sup> Table 1 summarizes other physical and chemical properties of Propyl Gallate.

### 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.

**TABLE 1.** Physical and Chemical Properties

| <i>Property</i>   | <i>Value</i>    | <i>Reference</i> |
|---|-----------------|------------------|
| Molecular weight  | 212.20          | 2                |
| Melting range   | 146-150°C       | 2,5              |
| Absorption wavelength (alcohol)                           | 275*            | 7,8              |
| pKa   | 8.11            | 9                |
| Partition coefficient (oleyl alcohol:water)               | 17              | 9                |
| Partition coefficient (octanol:water)                     | 32              | 9                |
| R <sub>M</sub>  | -0.52           | 9                |
| Ash   | 0.1 percent max | 5                |
| Loss on drying  | 0.5 percent max | 5                |
| Inorganic Impurities <sup>†</sup><br>(recommended levels) |                 |                  |
| As  | 3 ppm max       | 5                |
| Pb  | 20 ppm max      | 5                |
| pH 0.05 percent (aqueous)                                 | 6.3             | 10               |
| 0.1 percent (aqueous)                                     | 5.9             | 10               |
| 0.2 percent (aqueous)                                     | 5.7             | 10               |

\*Increasing Propyl Gallate concentration broadens curve to 290–320 nm.  
At 10 percent, absorption peak is greater than 390 nm.

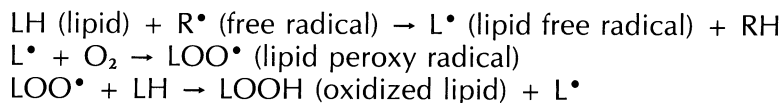
<sup>†</sup>No information is available on organic impurities.

**TABLE 2.** Analytical Methods Used in Propyl Gallate Determination

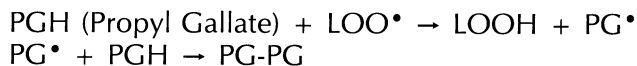
| <i>Method</i>                              | <i>Reference</i> |
|--|------------------|
| Paper chromatography                       | 13,14            |
| Thin-layer chromatography (TLC)            | 15–17            |
| Gas chromatography (GC)                    | 18               |
| Vacuum sublimation/GC                      | 19               |
| Reversed phase partition chromatography    | 20               |
| Centrifugal paper chromatography           | 13               |
| Polyamide TLC                              | 21,22            |
| Liquid chromatography                      | 23               |
| Electron capture/gas–liquid chromatography | 24,25            |
| Column chromatography                      | 20               |
| High performance liquid chromatography     | 26               |
| Infrared spectroscopy                      | 5                |
| Fluorometric analysis                      | 27               |
| Ultraviolet spectrophotometry              | 28,29            |
| Colorimetric analysis with Iron (II) ion   | 30,31            |
| Phosphomolybdic acid                       | 31               |
| 2,2'-Bipyridyl reagent                     | 32               |
| 2,2'-Diphenyl-1-picryl hydrazyl            | 33               |

### Reactivity

As an antioxidant, Propyl Gallate prevents the formation or accumulation of free radicals in a chemical or a biological system; hence, it is called a “free-radical scavenger.” Free radicals can be generated in these systems by irradiation, chemical reaction, oxidation, or enzymatic reactions. Propyl Gallate is often used to prevent the free-radical peroxidation of lipids. This lipoperoxidation reaction occurs as follows<sup>(11)</sup>:



The reaction proceeds naturally until all of the lipid is oxidized, which causes fats to become rancid and tissue to be damaged by irradiation. Propyl Gallate interferes with this reaction at the stage of lipid peroxy radical formation<sup>(11)</sup>:



The antioxidant activity of Propyl Gallate resides in the presence of its hydrogen-donating hydroxyl groups.<sup>(10)</sup> The oxidation of Propyl Gallate during free-radical scavenging occurs as is shown in Figure 1.<sup>(12)</sup>



Many of the above reactions with Propyl Gallate occur in biological systems. One important chemical system reaction is the inhibition by Propyl Gallate of nitrosopyrrolidine formation in cooked, nitrite-cured bacon.<sup>(34)</sup> Further details are given in the section, Biological Effects/Biochemical Reactions.

Propyl Gallate is stable in neutral or slightly acidic chemical environments but is unstable when heated or in mild alkaline environments.<sup>(35)</sup> It discolors in the presence of iron or when it is exposed to air or light for long periods of time.<sup>(36)</sup>

## USE

### Cosmetic

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. BHA and Propyl Gallate are synergistic antioxidants.<sup>(37)</sup>

According to the industry's voluntary submissions to the Food and Drug Administration (FDA) in 1981, Propyl Gallate alone was reported in 118 formulations at concentrations up to 5 percent (Table 3). Formulations commonly contain Propyl Gallate at concentrations of less than 0.1 percent. These data do not include the use of antioxidant mixtures containing Propyl Gallate, which were used in 848 cosmetic formulations in 1981.<sup>(38)</sup> These mixtures usually contain up to 6 percent Propyl Gallate and are used at low concentrations in almost all product type categories.<sup>(2,38,39)</sup>

The cosmetic product formulation computer printout made available by FDA is compiled through voluntary filing of such data in accordance with Title 21, part 720.4 of the Code of Federal Regulations. Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100 percent concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. The fact that data are submitted only within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

### 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 sol-

TABLE 3. Product Formulation Data<sup>(38)</sup>

| Product Category   | Total No. of Formulations in Category | Total No. Containing Ingredient | No. of Product Formulations Within Each Concentration Range (percent) |      |        |      |
|--|---------------------------------------|---------------------------------|---|------|--------|------|
|  |                                       |                                 | Unreported Concentration  | >1-5 | >0.1-1 | ≤0.1 |
| <i>Propyl Gallate</i>  |                                       |                                 |   |      |        |      |
| Bath oils, tablets, and salts  | 237                                   | 4                               | —   | —    | —      | 4    |
| Mascara  | 397                                   | 2                               | —   | —    | —      | 2    |
| Colognes and toilet waters   | 1120                                  | 5                               | —   | —    | —      | 5    |
| Perfumes   | 657                                   | 3                               | —   | —    | —      | 3    |
| Fragrance powders (dusting and talcum, excluding aftershave talc)            | 483                                   | 2                               | —   | 1    | —      | 1    |
| Other fragrance preparations   | 191                                   | 2                               | —   | —    | 2      | —    |
| Hair shampoos (noncoloring)  | 909                                   | 2                               | —   | —    | —      | 2    |
| Blushers (all types)   | 819                                   | 7                               | —   | —    | —      | 7    |
| Face powders   | 555                                   | 3                               | —   | —    | —      | 3    |
| Makeup foundations   | 740                                   | 2                               | —   | —    | —      | 2    |
| Lipstick   | 3319                                  | 21                              | —   | —    | —      | 21   |
| Makeup bases   | 831                                   | 1                               | —   | —    | —      | 1    |
| Rouges   | 211                                   | 1                               | —   | —    | —      | 1    |
| Makeup fixatives   | 22                                    | 1                               | —   | —    | —      | 1    |
| Other makeup preparations (not eye)  | 530                                   | 7                               | —   | —    | —      | 7    |
| Cuticle softeners  | 32                                    | 1                               | —   | —    | —      | 1    |
| Bath soaps and detergents  | 148                                   | 2                               | —   | —    | —      | 2    |
| Other personal cleanliness products  | 227                                   | 1                               | —   | —    | 1      | —    |
| Skin cleansing preparations (cold creams, lotions, liquids, and pads)        | 680                                   | 9                               | —   | —    | 1      | 8    |
| Face, body, and hand skin care preparations (excluding shaving preparations) | 832                                   | 11                              | —   | —    | —      | 11   |
| Moisturizing skin care preparations  | 747                                   | 9                               | —   | —    | —      | 9    |
| Night skin care preparations   | 219                                   | 4                               | —   | —    | 2      | 2    |
| Paste masks (mud packs)  | 171                                   | 1                               | —   | —    | —      | 1    |
| Skin lighteners  | 44                                    | 3                               | —   | —    | 1      | 2    |
| Skin fresheners  | 260                                   | 1                               | —   | —    | —      | 1    |
| Wrinkle smoothers (removers)   | 38                                    | 1                               | —   | —    | —      | 1    |
| Other skin care preparations   | 349                                   | 8                               | —   | —    | —      | 8    |
| Suntan gels, creams, and liquids   | 164                                   | 2                               | —   | —    | 1      | 1    |
| Indoor tanning preparations  | 15                                    | 1                               | —   | —    | —      | 1    |
| Other suntan preparations  | 28                                    | 1                               | —   | —    | —      | 1    |
| 1981 TOTALS  |                                       | 118                             | —   | 1    | 8      | 109  |

ubility of Propyl Gallate in fats and oils is limited to less than 2 percent. Propyl Gallate is often difficult to dissolve in these substances without the aid of a carrier solvent.<sup>(35,36,40)</sup>

Propyl Gallate is used at concentrations of 0.01484 to 0.00001 percent 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 FDA has placed the limit on the total antioxidant content of food at 0.02 percent of the fat or oil content of the food.<sup>(40)</sup>

A National Research Council Subcommittee has estimated the average daily intake of Propyl Gallate from foods 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. The Select Committee of the LSRO<sup>(40)</sup> concluded that these figures accurately reflect the actual amounts of Propyl Gallate consumed by these various groups.

An acceptable daily intake of Propyl Gallate for humans has been determined by the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives to be 0.2 mg/kg (unconditional) and 0.2 to 0.5 mg/kg (conditional). Additionally, the US Department of Agriculture (USDA) has determined that Propyl Gallate is an acceptable antioxidant for use in meat products (within specified limits).<sup>(40)</sup>

Propyl Gallate is used as a direct food additive in 12 European countries, as well as Canada, Australia, South Africa, and Russia at concentrations up to 2.0 percent.<sup>(41)</sup>

## BIOLOGICAL EFFECTS

### Antimicrobial Activity

Jordan et al.<sup>(42)</sup> studied the antibacterial effects of Propyl Gallate on bacteria of the human oral cavity. At concentrations of 0.0032 to 0.266 percent, Propyl Gallate inhibited the growth of 27 strains of bacteria. 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.<sup>(43)</sup> Shih and Harris<sup>(44)</sup> observed Propyl Gallate, at 400 ppm, to be lethal to *Escherichia 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.

The effect of Propyl Gallate on *E. coli* was further studied in 1979 by Boyd and Beveridge. The antibacterial activity of this ingredient 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.

Propyl Gallate stabilizes oxidation-sensitive amphotericin-B and prolongs its antifungal activity. An antifungal synergism between these two compounds has been suggested.<sup>(45,46)</sup>

Propyl Gallate inhibited the multiplication of the virus of nuclear polyhedral disease in silkworms by inducing a decreased oxygen requirement, inhibiting penetration of the virus into cells, inhibiting viral DNA synthesis, and by reducing the DNA and RNA content of the silkworm cells.<sup>(47)</sup>

### Biochemical Reactions

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 regenerated. Photodynamic activation occurred with the formation of a free radical, and Propyl Gallate acted by inhibiting free-radical formation.<sup>(48)</sup>

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.<sup>(49)</sup>

Gonikberg et al.<sup>(50)</sup> reported that Propyl Gallate forms a biochemical complex with flavinmononucleotide (FMN).

### Inhibition of Formation of Carcinogenic Nitrosamines

Kawanishi et al.<sup>(51)</sup> found that Propyl Gallate inhibited nitrosamine formation from aminopyrine and sodium nitrite in rat stomachs. Inhibition was as high as 55 percent at a dose of 100  $\mu$ mol Propyl Gallate per kg body weight; Propyl Gallate was considered a relatively strong inhibitor. Similarly, Rao et al.<sup>(52)</sup> 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 percent at pH 3.

### Effects on Enzymes and Enzyme Systems

Free radicals are generated at almost all stages of glycolysis, respiration, oxidation, and certain enzyme systems, among other biochemical processes. Since 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.<sup>(53)</sup> Vartanyan et al.<sup>(54)</sup> 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 ( $7.1 \times 10^{-4}$  M). Brzhevskaya et al.<sup>(55)</sup> reported that Propyl Gallate, at concentrations of  $1 \times 10^{-3}$  M to  $6.7 \times 10^{-3}$  M, inhibited the enzymatic hydrolysis of adenosine triphosphate (ATP) 40 to 85 percent by blocking the formation of free radicals. Agatova and Emanuel<sup>(56)</sup> stated that radicals of Propyl Gallate (at concentration of  $1 \times 10^{-3}$  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 RNA-ase 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.<sup>(57)</sup>

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.<sup>(58)</sup> Yang and Strickhart<sup>(59)</sup> observed that Propyl Gallate inhibited microsomal benzo[a]pyrene hydroxylase and demethylase activities in vivo, with 50 percent inhibition occurring at 50 and 140 to 500  $\mu$ M 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<sup>(58)</sup> had suggested. The authors believed the site of inhibition was cytochrome P-450 itself. In 1977, Rahimtula et al.<sup>(60)</sup> confirmed that Propyl Gallate (25 to 125  $\mu$ M) did not inhibit NADPH-cytochrome P-450 reductase but did inhibit benzo[a]pyrene hydroxylase.

The conflicting in vitro results reported by Torrielli and Slater<sup>(58)</sup> and Yang and Strickhart<sup>(59)</sup> may mean that the concentrations of Propyl Gallate attained in vivo were much lower than those used in vitro.<sup>(61)</sup>

Further studies revealed that Propyl Gallate inhibited three azoreductases of the hepatic microsomal mixed function oxidase system,<sup>(62)</sup> epoxidation of all-trans-retinoic acid by rat tissue homogenate,<sup>(63)</sup> particulate guanylate cyclase activity from fibroblast and liver homogenates by preventing arachidonate oxidation and malonyldialdehyde formation,<sup>(64)</sup> and glucose-6-phosphatase activity in rat microsomes both in vivo and in vitro.<sup>(65)</sup>

Propyl Gallate, which is metabolized to a substrate for Phase II xenobiotic metabolizing enzymes (glucuronide formation) in the liver, was injected 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.<sup>(66)</sup>

The effect of Propyl Gallate on the hepatic mixed-function oxidase system was studied in weanling rats. Animals were placed on diets containing various amounts and types of fat plus 0 or 0.3 percent 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: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.

### Endocrinological Effects

Propyl Gallate was reported to inhibit the biosynthesis of prostaglandin (PGE) from seminal vesicles and mammary glands. Nugterin et al.<sup>(67)</sup> were first to demonstrate that high concentrations of Propyl Gallate inhibited prostaglandin synthesis in sheep seminal vesicles. McDonald-Gibson et al.<sup>(68)</sup> confirmed these findings (50 percent inhibitory concentration of 103  $\mu$ M) using bull seminal vesicles in vitro. Panganamala et al.<sup>(69)</sup> reported that Propyl Gallate, at concentrations of  $4 \times 10^{-4}$  M, inhibited the formation of prostaglandin from eicosa-8,11,14-trienoic acid by bovine seminal vesicle microsomes.

Beetens and Herman<sup>(70)</sup> observed that Propyl Gallate enhanced the formation of 6-oxo-PGF<sub>1 $\alpha$</sub>  by incubation with ram seminal vesicle microsomes. This resulted either from stimulation of prostacyclin synthetase or from inhibition of a prostacyclin synthetase inhibitor.

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.<sup>(69)</sup>

The effect of Propyl Gallate on prostaglandin synthetase activity of mammary gland tissue was studied in vivo. Female Sprague-Dawley rats were fed diets containing various lipid content, with or without Propyl Gallate (0.3 percent). Rats were killed 24 hours later, and homogenates of mammary gland tissues were prepared for prostaglandin synthetase determination. Dietary Propyl Gallate produced an elevation of PGF<sub>2 $\alpha$</sub>  but had no effect on PGE<sub>2</sub>. It was suggested that Propyl Gallate scavenged the oxygen radical formed during the conversion of PGG<sub>2</sub> to PGH<sub>2</sub> and, consequently, altered the amount and types of prostaglandins produced by the mammary gland.<sup>(71)</sup>

Propyl Gallate altered prostaglandin endoperoxide synthetase and peroxidase activities of seminal vesicle microsomes. At 0.1 mM Propyl Gallate, production of PGF<sub>2 $\alpha$</sub>  and PGE<sub>2</sub> by mammary gland tissue microsomes was stimulated, but at higher concentrations (0.50 to 2.50 mM) inhibition occurred. Mammary gland tissue microsomes of rats fed diets containing 0.3 percent Propyl Gallate synthesized more PGF<sub>2 $\alpha$</sub>  and PGI<sub>2</sub> than did controls. Exogenous Propyl Gallate stimulated production of PGF<sub>2 $\alpha$</sub>  and PGE<sub>2</sub> 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.<sup>(72)</sup>

### Cellular/Tissue Effects

Propyl Gallate stimulated the growth of human diploid fibroblasts at a concentration of  $10^{-8}$  M; however, it was a potent inhibitor of the same at concentra-

tions of  $10^{-6}$  M or greater.<sup>(73)</sup> Propyl Gallate also inhibited in vitro antibody production by mouse splenic cells at 5  $\mu\text{g/ml}$  and suppressed multiplication of human and mouse cells at 20  $\mu\text{g/ml}$ .<sup>(74)</sup>

The effect of Propyl Gallate on mouse lung metabolism was studied by Omaye et al.<sup>(75)</sup> Groups of 16 to 24 adult mice were given single intraperitoneal injections 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.

### 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.<sup>(76)</sup>

Modak and Rao<sup>(77)</sup> 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 percent in saline) was injected intradermally into the epilated skin of each animal. Procaine HCl was injected in other sites of the same animal to compare the response to Propyl Gallate. Pinprick reaction in these injection sites was 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 4 rabbits. Results of these tests indicated that Propyl Gallate possessed good local anesthetic activity when compared to a known anesthetic (Procaine). The activity of Propyl Gallate in infiltration anesthesia was potentiated by epinephrine.

The effect of Propyl Gallate on arachidonic acid (AA)-induced abdominal contractions was studied 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  $\mu\text{g/ml}$  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.<sup>(68)</sup>

### Special Studies

#### Ionizing/Ultraviolet Radiation Protection

Ionizing radiation results in excessive peroxide formation in animal tissue; these peroxides are, in turn, tissue damaging. Propyl Gallate demonstrated a protective effect against radiation in mice administered Propyl Gallate orally (0.25 to

0.5 percent in the diet) or intraperitoneally (30 to 150 mg/kg) and in rats administered intraperitoneally (50 mg/kg) prior to exposure to sublethal doses of radiation.<sup>(78-81)</sup>

It was determined that Propyl Gallate inhibited DNA depolymerization induced by ionizing radiation in vitro.<sup>(79-82)</sup> Pre- or posttreatment with Propyl Gallate increased the survival rate of monkey heart cells in vitro following gamma-radiation.<sup>(83)</sup> Sheng et al.<sup>(84)</sup> 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.<sup>(85)</sup> This result prompted Kahn et al.<sup>(8)</sup> 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 react 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 *Salmonella 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.<sup>(86)</sup>

The effect of Propyl Gallate as an ultraviolet light protector was studied in vivo by McDonald-Gibson and Schneider.<sup>(87)</sup> The test material (up to 10 percent w/w) was applied to the epilated ear of guinea pigs either before or after UV radiation. In unprotected sites, radiation resulted in erythema, edema and blister formation. Pretreatment with Propyl Gallate inhibited induction of erythema, edema, and pyresis. Posttreatment 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 hours later. When compared to control sites, Propyl Gallate reduced UV light-induced erythema. This effect may be linked to its inhibition of prostaglandin synthesis.<sup>(88)</sup>

### 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 ( $\text{CCl}_4$ ), hepatotoxicity (acetaminophen), fatty liver (white phosphorus,  $\text{CCl}_4$ ), hepatic polysomal disaggregation (white phosphorus), hemolysis of RBCs (vitamin  $\text{D}_2$ ), and decreased hepatic microsome amino acid incorporation ( $\text{CCl}_4$ ). 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.<sup>(89-97)</sup>

### 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.<sup>(98)</sup> In two studies, Propyl Gallate (25 to 125  $\mu$ M and 410 nmol/plate) inhibited the mutagenic activity of benzo[a]pyrene (BP) metabolites in *S. typhimurium* strain TA98.<sup>(60,99)</sup> Rahimtula et al.<sup>(60)</sup> claimed that Propyl Gallate inhibited BP-hydroxylase in the microsomal preparation. Springarn and Garvie<sup>(100)</sup> 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.<sup>(101)</sup> 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.<sup>(102)</sup> In addition, Propyl Gallate reduced the mutagenic activity of aflatoxin B<sub>1</sub> in *S. typhimurium* TA98 under metabolic activation,<sup>(103)</sup> but in a similar study, it slightly increased (by 50 to 100 percent at highest dose tested) the mutagenic effect of this carcinogen in *S. typhimurium* TA100.<sup>(104)</sup>

### Anticarcinogenesis/Antitumorigenesis

Kozumbo et al.<sup>(105)</sup> 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  $\mu$ mol) applied topically to mouse epidermis substantially inhibited TPA-induced ODC activity. Propyl Gallate may inhibit the promotion phase of carcinogenesis.

McCay et al.<sup>(106)</sup> 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 percent 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.

### Anticancer

Emanuel et al.<sup>(107)</sup> 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 percent) 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.<sup>(108)</sup> 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.

In 1961, Emanuel stated that Propyl Gallate can act specifically to suppress glycolysis, as well as the activities of cytochrome oxidase and many dehydrogenases. Kukushkina et al.<sup>(109,110)</sup> reported that Propyl Gallate inhibited protein and nucleic acid biosynthesis in Ehrlich 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.<sup>(111)</sup> reported that Propyl Gallate inhibited RNA formation in Ehrlich ascites carcinoma cell preparations. This effect probably was due to the interaction of Propyl Gallate with the SH groups of enzymes involved with RNA transcription.

Propyl Gallate has been shown to have either a radioprotective or a radiosensitizing effect, depending on the duration of its action before radiation. Aphanasjev et al.<sup>(112)</sup> first reported the radiosensitizing 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,<sup>(113)</sup> in experiments with isolated DNA, reported that the radioprotective effect of Propyl Gallate increased as the concentration of unoxidized Propyl Gallate (maximum effect at  $1.65 \times 10^{-2}$  M) increased before radiation and likewise the radioprotective effect decreased as the time of pre-irradiation 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.

### Antiteratogenesis

Propyl Gallate inhibition of teratogenesis by certain chemicals has been studied. 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 percent along with doses of 0 to 10 mg/rat vitamin E. On the twenty-first day of gestation, the rats were killed and the fetuses were examined. At 0.025 percent, Propyl Gallate did not reduce the frequency of vitamin E deficiency-induced malformations; at 0.4 percent alone or at lower concentrations with vitamin E supplements, Propyl Gallate reduced the teratogenic effects.<sup>(114)</sup>

Desesso<sup>(115)</sup> studied the effect of Propyl Gallate on hydroxyurea (HU)-induced teratogenesis. Various amounts of Propyl Gallate (362–906 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 com-

pounds. 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. Desso suggested that the antioxidant properties of Propyl Gallate acted within the embryo to reduce the severity of HU teratogenesis.

### **Anticariogenesis**

In the 1960s, the effect of Propyl Gallate on caries was studied extensively. Jordan et al.<sup>(42)</sup> placed rats on cariogenic diets with and without 0.5 percent 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 reduced 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. Thus, Propyl Gallate acts as an antibacterial agent in reducing caries.

Lisanti and Eichel<sup>(116)</sup> studied the cariogenic effect in hamsters. Groups of 40 animals were fed control or cariogenic diets, which included 0 or 0.03 percent 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 reduced the number of caries when compared to positive and negative controls. Total number of caries was reduced by 60 percent in male rats and by 36 percent in female rats. Therefore, 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.<sup>(117)</sup> reported the results of a 30-day study of Propyl Gallate in cotton rats. Groups of 16 animals were fed a cariogenic diet containing 0.5 percent 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 reduce the incidence of caries. Propyl Gallate-fed rats had a significantly higher incidence of caries when compared to controls.

### **Absorption, Metabolism, and Excretion**

Orten et al.<sup>(118)</sup> analyzed the urine from dogs fed diets containing 0.0117 percent Propyl Gallate for 14 months. During this time, no detectable quantities of Propyl Gallate were found in the urine. Van Esch<sup>(119)</sup> 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 hours.

Dacre<sup>(120)</sup> and Booth et al.<sup>(121)</sup> studied extensively 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

percent of the administered dose was excreted in the urine, 72 percent as 4-methoxygallic acid glucuronide (4-methoxygalloyl- $\beta$ -D-glucosiduronic acid) and 6.7 percent as unconjugated phenolic compounds. Minor metabolites included pyrogallol (free and conjugated) and free 4-methoxy gallic acid. Figure 2 represents the metabolic pathway of Propyl Gallate in rats and rabbits.

## ANIMAL TOXICOLOGY

### Acute Effects

#### Oral Toxicity

The acute oral LD<sub>50</sub> 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 indicate that ingested Propyl Gallate is, at worst, slightly toxic (Table 4).

Three lipstick formulations were evaluated by an acute oral toxicity study using rats. The test material was given by gastric intubation. No deaths occurred in the separate tests of two lipstick formulations containing 0.005 percent Propyl Gallate up to an exposure of 5.0 g/kg of the formulation.<sup>(122,123)</sup> The third formulation, containing less than 1 percent 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.<sup>(124)</sup>

Two suntan preparations, a sun protection stick and a suntan cream, each containing 0.003 percent Propyl Gallate, were evaluated by acute oral toxicity studies. Both were administered by gavage to 10 rats. The sun protection stick was administered as a 50 percent 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.<sup>(125,126)</sup>

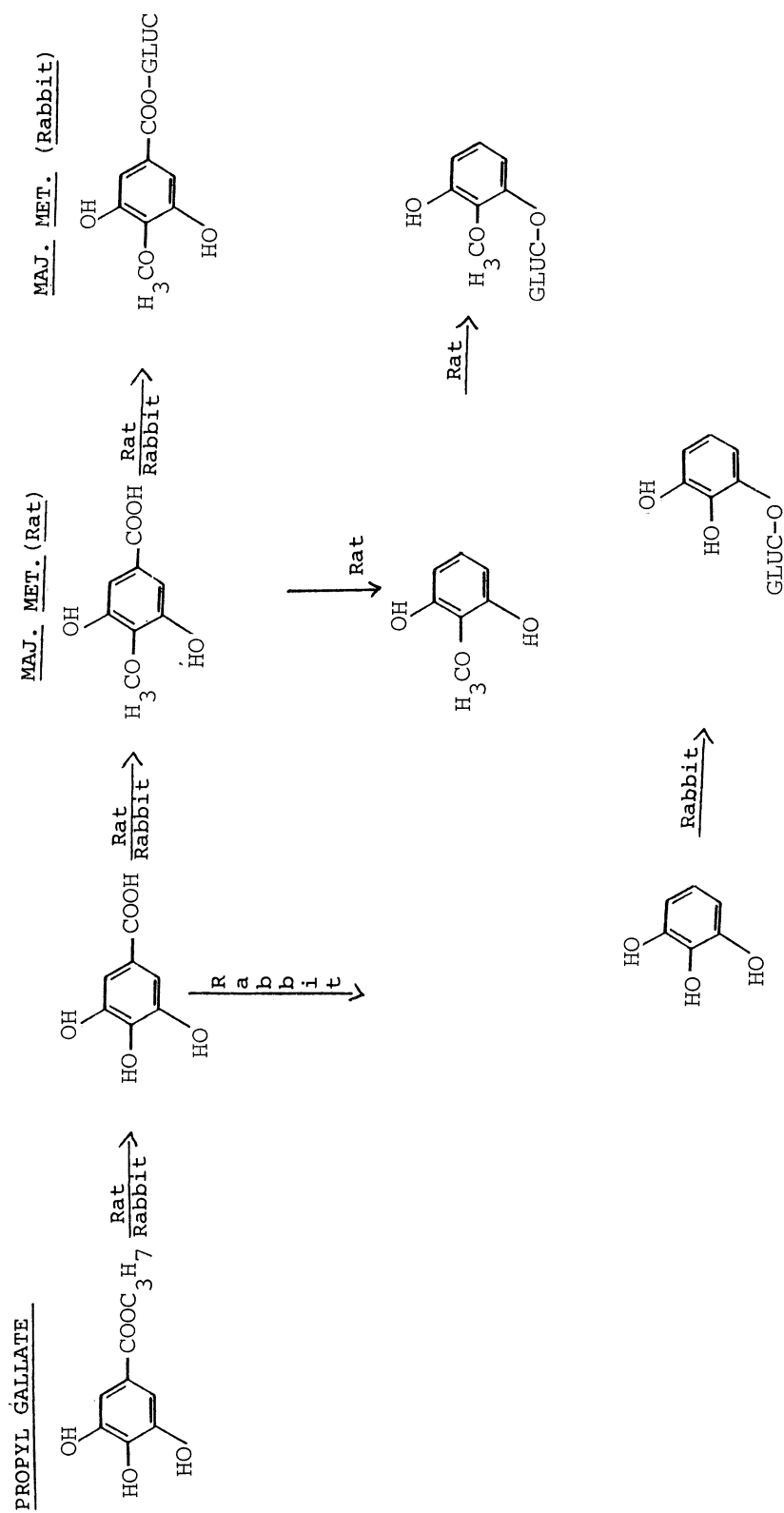
#### Intraperitoneal Toxicity

The acute intraperitoneal (IP) 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 IP LD<sub>50</sub> was determined to be 0.38 g/kg. Death usually occurred within 10 to 60 minutes postinjection 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.<sup>(118)</sup>

#### Primary Skin Irritation

Propyl Gallate was practically nonirritating to rabbit and guinea pig skin in five tests using concentrations as high as 10 percent (in propylene glycol) and as low as 0.003 percent (in a formulation) (Table 5).





**FIG. 2.** Metabolic pathway of Propyl Gallate in rats and rabbits.

**TABLE 4.** Acute Oral Toxicity of Propyl Gallate

| <i>Animal</i> | <i>Number/<br/>Group</i> | <i>Dose<br/>(g/kg)</i> | <i>LD<sub>50</sub><br/>(g/kg)</i> | <i>Comment/Conclusion*</i>   | <i>Reference</i> |
|---------------|--------------------------|------------------------|-----------------------------------|--|------------------|
| Mouse         | 6–10                     | 1–4                    | 2.00                              | Slightly toxic   | 10               |
| Mouse         | —                        | —                      | 3.50                              | Slightly toxic   | 127              |
| Mouse         | —                        | 0.5–2.5                | 1.70                              | Slightly toxic   | 128              |
| Mouse         | —                        | —                      | 2.85                              | Slightly toxic   | 40               |
| Rat           | —                        | 0.5–3.5                | 2.60                              | Slightly toxic   | 128              |
| Rat           | —                        | —                      | 3.60                              | Slightly toxic   | 120              |
| Rat           | 2–18                     | 2–5                    | 3.8                               | Slightly toxic—death due to asphyxia or cardiorespiratory failure; autopsy revealed dilatation of visceral and peripheral blood vessels and inflated lungs | 118              |
| Rat           | —                        | —                      | 3.00                              | Slightly toxic   | 40               |
| Rat           | —                        | —                      | 2.50                              | Slightly toxic   | 129              |
| Rat           | —                        | —                      | 5–7                               | Practically nontoxic—in dead animals, pathological effects in the kidneys  | 119              |
| Rat           | —                        | —                      | 4                                 | Slightly toxic   | 130              |
| Rat           | 5                        | 0.10–4.0               | 2.1                               | Slightly toxic—autopsy of dead animals revealed pleural fluid and distended intestine  | 131              |
| Rat           | 10                       | 5                      | > 5                               | Practically nontoxic—no deaths   | 131              |
| Hamster       | —                        | —                      | 2.48                              | Slightly toxic   | 40               |
| Rabbit        | —                        | —                      | 2.75                              | Slightly toxic   | 40               |
| Pig           | —                        | 2–6                    | > 6                               | Practically nontoxic—no deaths   | 119              |

\*According to Hodge, H.C., and Sterner, J.H. (1949). Tabulation of toxicity classes. *Am. Indust. Hyg. A. Quart.* **10**, 93–6.

In an early study, a 10 percent 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<sup>(10)</sup> (Table 5).

Propyl Gallate, at concentrations of 0.5 and 1.0 percent in saline, was injected intradermally into the shaved skin of each of 3 albino rabbits. Positive and negative controls were also 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 percent resulted in a mean irritation score of 2 (maximum score = 16), indicating that Propyl Gallate was practically nonirritating to local tissue<sup>(77)</sup> (Table 5).

A primary skin irritation test on the intact and abraded skin of 6 rabbits was conducted using a lipstick formulation containing less than 1 percent Propyl Gallate. The test material was applied for 24 hours under an occlusive wrap. Upon removal of the wrap, the test sites were scored for erythema and edema at 24 and 72 hours. No erythema was observed. A very slight edema at 3 intact and 3 abraded sites and a slight edema at 1 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 considered not a primary irritant<sup>(132)</sup> (Table 5).

A primary skin irritation test was conducted to evaluate a suntan cream containing 0.003 percent Propyl Gallate. Test samples weighing 0.5 g were applied

TABLE 5. Primary Skin Irritation of Propyl Gallate

| Compound   | Type of Test   | No. of Animals                 | Results/Comments   | Reference |
|--|--|--------------------------------|--|-----------|
| Propyl Gallate—10 percent solution in propylene glycol         | Applied to shaved skin for 48 hours                                | Unspecified no. of guinea pigs | No local lesions or primary irritation   | 10        |
| Propyl Gallate—0.5 percent and 1.0 percent solutions in saline | Intradermal injection  | 3 rabbits                      | Score of 2 (max = 16); practically nonirritating to local tissue   | 77        |
| Propyl Gallate—<1 percent in a lipstick                        | Primary skin irritation—intact and abraded, 24 hour application    | 6 rabbits                      | PII* = 0.33 (max = 8); not a primary irritant  | 132       |
| Propyl Gallate—0.003 percent in a suntan cream                 | Primary skin irritation—intact and abraded, 3 24-hour applications | 6 rabbits                      | 5 rabbits exhibited grade 1 erythema (max = 4) at 48 and 72 hours; no edema; not a primary skin irritant | 133       |
| Propyl Gallate—0.003 percent in a suntan oil                   | Primary skin irritation—intact, 3 6-hour applications              | 6 rabbits                      | One score of 1 (max = 8) at 48 hours and at 72 hours; practically nonirritating                          | 134       |

\*PII, Primary Irritation Index.

to the intact and abraded skin of each of 6 rabbits. Sites were washed and rinsed after 24 hours and reactions scored 30 minutes later. This procedure was repeated for three applications. Five rabbits had grade 1 erythema (scale of 0 to 4) at 48 and 72 hour readings; no edema was reported. The suntan cream was not a primary skin irritant<sup>(133)</sup> (Table 5).

A modified Draize skin irritation test was used to evaluate a suntan oil containing 0.003 percent Propyl Gallate. Test samples of 0.5 ml were applied to the shaved skin of each of 6 rabbits. Sites were washed and rinsed after 6 hours and reactions scored 30 minutes later. Similar applications were made on the following 2 days. Average scores of 1 (scale of 0 to 8) were found in 1 rabbit at 48 hours and 1 at 72 hours. The suntan oil was practically nonirritating under the test conditions<sup>(134)</sup> (Table 5).

### Acute Eye Irritation

Propyl Gallate was nonirritating to rabbit eyes in 9 tests of cosmetic formulations containing less than 1 percent Propyl Gallate (Table 6).

An acute eye irritation test on 6 rabbits was conducted using a lipstick formulation containing less than 1 percent 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 1 rabbit was reported. The latter was graded as a response of 2 (maximum score of 110). The lipstick formulation was not an eye irritant<sup>(135)</sup> (Table 6).

Two suntan preparations, a sun protection stick and a suntan cream, each containing 0.003 percent Propyl Gallate, were tested for acute eye irritation by the Draize technique.<sup>(136)</sup> A 0.1 g sample of each product (full strength) was instilled into the conjunctival sac of 9 rabbits. Three rabbits received no further treatment, the eyes of the second 3 were rinsed with water 2 seconds after instillation, and the eyes of the third 3 were rinsed 4 seconds after instillation. Reactions were scored at 24, 48, and 72 hours 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 hours. Only 2 rabbits had conjunctival irritation at 48 hours, and all eyes were clinically normal at 72 hours. Five of the nine rabbits receiving the suntan cream showed conjunctival irritation (1 on a scale of 0 to 3), and 2 had chemosis (1 on a scale of 0 to 4) at 24 hours. All eyes were normal at 48 hours. The products were not eye irritants<sup>(137,138)</sup> (Table 6).

**TABLE 6.** Acute Eye Irritation of Products Containing Propyl Gallate

| Product                      | Concentration<br>of Propyl<br>Gallate<br>(percent) | Test<br>Method    | No. of<br>Animals            | Results/<br>Comments | Reference |
|------------------------------|--|-------------------|------------------------------|----------------------|-----------|
| Lipstick                     | <1   | Draize            | 6 rabbits                    | Nonirritant          | 135       |
| Sun protection<br>stick      | 0.003  | Draize            | 9 rabbits                    | Nonirritant          | 137       |
| Suntan cream                 | 0.003  | Draize            | 9 rabbits                    | Nonirritant          | 138       |
| 6 Cosmetic formu-<br>lations | 0.003 in each<br>formulation                       | 16 CFR<br>1500.42 | 6 rabbits per<br>formulation | Nonirritants         | 139,140   |

Six cosmetic formulations, each containing 0.003 percent Propyl Gallate, were tested for eye irritation as described in 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 6 rabbits also served as an untreated control. Reactions were scored on a standard Draize scale at 24, 48, and 72 hours and 7 days. The formulations produced no or very slight irritations, all of which progressively decreased to a 0 score at 72 hours. None of these formulations were eye irritants<sup>(139,140)</sup> (Table 6).

## Subchronic Effects

### Cutaneous Toxicity

Cutaneous toxicity was studied using Propyl Gallate, 20 percent in lanolin, applied daily, 5 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 microscopic examination. Treatment with Propyl Gallate resulted in reversible hyperplasia of the epidermis.<sup>(141)</sup>

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 0.1 to 10 percent to the epilated dorsal skin of groups of 2 to 5 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.<sup>(142)</sup>

### Oral Toxicity

Rats and pigs (strain/breed and number not specified) were fed diets containing 0.035 to 0.5 percent and 0.2 percent 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.<sup>(119)</sup>

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.<sup>(128)</sup>

Six groups of 12 weanling rats each were fed diets containing 0 to 0.5 percent 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. Weights of the liver and adrenal gland were normal, and no pathologic changes could be attributed to treatment. Propyl Gallate had an insignificant effect on serum concentration of cholesterol and sodium, on the cholesterol content of the adrenal gland, and lipid content of the liver. Propyl Gallate did not produce significant toxic effects in rats when ingested and was considered safe for use in food.<sup>(143)</sup>

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.<sup>(144)</sup>

Four groups of 8 rats each and one group of 7 rats received doses of 0 to 500 mg/kg per day Propyl Gallate by stomach tube for 1 week. Animals were killed 24 hours after the final dosing. Four additional groups of 6 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 hours after the final dosing, but the severity decreased significantly after 14 days of recovery. By 28 days, the liver 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 twenty-eighth day posttreatment.<sup>(145)</sup>

### Sensitization

Three separate tests were used to determine the sensitizing potential of Propyl Gallate in guinea pigs. In the first test, Propyl Gallate (5 percent in complete Freund's adjuvant) was administered intradermally every other day for 6 days into the clipped dorsal skin of 2 female guinea pigs. Ten days after the last injection, occlusive patches containing 0.1, 0.5, and 2 percent Propyl Gallate in alcohol were each applied to the clipped ventral skin for 24 hours. Sites were scored at 24 and 48 hours. No sensitization occurred at 0.1 percent, but it did occur at the other 2 test concentrations. Reactions gradually subsided within 7 to 10 days. Tests performed 3 months later 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.<sup>(146)</sup>

In the second study, 20 percent Propyl Gallate in alcohol was applied for 24 hours under occlusion to clipped shoulder skin of 2 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 percent Propyl Gallate were applied to the clipped ventral skin for 24 hours. Sites were scored at 24 and 48 hours. Mild to moderate irritation was produced by 1 and 5 percent Propyl Gallate at 24 hours and by 5 percent at 48 hours. When animals were retested 3 months later, severe reactions were observed.<sup>(146)</sup>

In the third study, 10 percent 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 percent Propyl Gallate and 0.05 percent dinitrochlorobenzene (DNCB) in complete Freund's adjuvant into the clipped dorsal skin, every other day for 6 days. Additionally, a group of 2 animals received the intradermal injections but did not participate in the Propyl Gallate feeding induction. Ten days after the final injection, 24-hour occlusive challenge patches containing 0.1, 0.5, or 2 percent Propyl Gallate and 0.1, 0.05, or 0.01 percent DNCB were applied to previously untested skin sites.

Sites were scored at 24 and 48 hours. 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 percent or 2 percent Propyl Gallate, respectively. At 0.1 percent, Propyl Gallate was nonsensitizing.<sup>(146)</sup>

Results of these three studies indicated 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.<sup>(146)</sup>

### Chronic Oral Toxicity

Ten groups of 10 to 20 weanling albino rats were fed diets containing either 0, 0.00117 to 2.34 percent Propyl Gallate, or an antioxidant mixture containing 2 percent 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 percent 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 lowered for these animals, growth returned to normal. No other gross effects were observed. Animals of the 1.17 and 2.34 percent Propyl Gallate groups had significantly lower 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 percent groups. Rats fed these concentrations also had significantly higher mortality rates.<sup>(118)</sup>

Two groups of 20 guinea pigs each (14 males and 6 females) were fed diets containing 0 or 0.0117 percent Propyl Gallate for 14 to 15 months. Males and females were mated within each group after 1 year of feeding; 6 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.<sup>(118)</sup>

Two groups of 5 and 7 dogs were fed diets containing 0 and 0.0117 percent Propyl Gallate, respectively, for 14 months. No alterations in behavior, appearance, and 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.<sup>(118)</sup>

The effect of Propyl Gallate on mortality was studied in rats. Six groups of 16 animals each were fed diets containing 0 to 5 percent 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 alive 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 percent Propyl Gallate diet. Propyl Gallate was concluded to be safe for use in foods.<sup>(147)</sup>

Seven groups of 26 rats each were fed diets containing bread made with vari-

ous concentrations of anti-oxidants, 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, 3 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.<sup>(39)</sup>

In a subsequent study, the investigators 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 tissue weight were found attributable to the ingestion of up to 20.25 mg Propyl Gallate per kg diet.<sup>(148)</sup>

Groups of rats and pigs (strain/breed unspecified) were given 0.035 to 0.5 percent and 0.2 percent Propyl Gallate, respectively, in the diet 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 that could be attributed to ingestion of Propyl Gallate were observed at necropsy. In older rats at 0.035 percent 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 percent Propyl Gallate diet, organ weights and hematologic values did not differ significantly from controls.<sup>(119)</sup>

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.<sup>(149)</sup>

Three groups of 50 albino mice each were fed diets containing 0, 0.5, or 1.0 percent Propyl Gallate for 90 weeks. Body weights, feed consumption, and hematological parameters were monitored. All surviving mice were killed and necropsied at 21 months. 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 percent 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.<sup>(118)</sup> corresponded to an intake of 0.05 g/kg per day.<sup>(150)</sup>

### Phototoxicity

A phototoxicity test was used to evaluate a sun protection stick containing 0.003 percent Propyl Gallate. The product was applied full strength to one of the tape-stripped ears of each of 6 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 hours to UVA from two GE F8T5-BL lamps at a distance of 4 to 6 cm. Ears were evaluated for irritation 24 and 48 hours later. No irritation was seen in any of the 6 guinea pigs. The sun protection stick was not phototoxic under these test conditions.<sup>(151)</sup>

### Mutagenesis

Three different assays, a host-mediated assay, a cytogenic assay, and a dominant lethal assay, were used 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* strain TA 1530 and G 46, as well as 2 ml *S. cerevisiae* strain D 3 indicator organisms. Animals were killed 3 hours 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 minutes 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.<sup>(131)</sup>

The cytogenic 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 hours. Bone marrow was removed, and the chromosome preparations were scored for abnormalities. Positive and negative controls were used. In the subchronic study, groups of 5 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.<sup>(131)</sup>

In the 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 2 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.<sup>(131)</sup>

A chromosomal aberration assay was used to study the activity of Propyl Gallate. The test material was added to cultures of Chinese hamster fibroblast cells at

doses up to 0.04 mg/ml in saline. Chromosome preparations were made 24 hours later. Propyl Gallate induced gaps, breaks, exchanges, and fragmentations in 20 percent of the cells at a dose of 0.023 mg/ml. The authors found that this compound produced significant aberrations under these test conditions.<sup>(152)</sup>

The cytogenetic activity of Propyl Gallate was tested in a diploid human embryo fibroblast cell line. Propyl Gallate was added to cell cultures at doses of 0 to 0.0212 mg/ml for 26 to 48 hours. 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 dose (0.0021 mg/ml), Propyl Gallate did not induce significant chromosomal aberrations or sister chromatid exchanges.<sup>(153)</sup>

In an Ames test, Propyl Gallate was tested for mutagenic activity in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, as well as *E. coli* strain WP2 at concentrations 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.<sup>(154)</sup>

In another Ames test, Propyl Gallate was added 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.<sup>(103)</sup>

Shelef and Chin<sup>(104)</sup> 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. Whereas Propyl Gallate was toxic to cells at the highest dose tested, no mutagenicity was found both with and without metabolic activation.

In a Japanese study, 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. 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.<sup>(155)</sup>

### Mutagenesis Enhancement

Rosin and Stich<sup>(103)</sup> reported that Propyl Gallate enhanced the mutagenic effect of N-hydroxy-2-acetylaminofluorene 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 percent increase in mutation frequency was observed without metabolic activation only. Propyl Gallate also induced a 700 percent increase in the mutagenic frequency of 4-NQO in TA98 and was also toxic to cells (only 16 percent cell survival). Therefore, Propyl Gallate may enhance the reduction of 4-NQO to a mutagenic product.

### Carcinogenesis and Tumorigenesis

Propyl Gallate was tested 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, 3 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.<sup>(156)</sup>

Propyl Gallate was tested for carcinogenicity by the National Toxicology Program (NTP) 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. Propyl Gallate was not considered to be carcinogenic in either species, although the increased number of malignant lymphomas in male mice may have been related to the administration of Propyl Gallate.<sup>(157)</sup>

### Teratogenesis

The teratogenic effect of Propyl Gallate was studied in 9 female rats by Telford et al.<sup>(158)</sup> Animals were mated and then given a total dosage of 0.5 g per rat in the diet. On the twenty-second 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 percent resorption; 77.7 percent litters with resorptions) when compared to controls (10.6 percent resorption; 40.8 percent litters with resorptions).

The teratogenic effects of Propyl Gallate were studied in 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 Day 6 to Day 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 weight was 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.<sup>(159)</sup>

A similar teratological study was performed on 4 groups of 20 to 50 pregnant rabbits given orally 2.5 to 250 mg/kg Propyl Gallate daily from Day 6 to Day 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.<sup>(160)</sup>

Desesso<sup>(115)</sup> studied the teratological effects of Propyl Gallate on rabbits. Each rabbit received a subcutaneous injection of 634 mg/kg Propyl Gallate in a water-ethanol vehicle on the twelfth gestational day. Two control groups were kept, one receiving the vehicle and the other remaining untreated. On the twenty-ninth day, the rabbits were killed and examined for resorptions and fetuses. No malformations and a low incidence of resorption were found in the 6 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.

In another teratogenesis study, groups of 18 to 20 pregnant Wistar rats were fed diets containing 0, 0.4 percent (0.35 g/kg), 1 percent (0.88 g/kg), or 2.5 percent (2.04 g/kg) Propyl Gallate starting on Day 1 of gestation. On the twentieth day of gestation, 13 of 18 rats of the 2.5 percent 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. The only possible compound-related finding was a significant number of fetuses obtained from the 2.5 percent 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 percent 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.<sup>(130)</sup>

## CLINICAL ASSESSMENT OF SAFETY

### Irritation and Sensitization

Propyl Gallate was essentially nonirritating and nonsensitizing to human skin in 13 tests (868 subjects) of cosmetic formulations containing less than 1 percent

Propyl Gallate. Propyl Gallate applied at 10 percent in propylene glycol produced no irritation, although applications at 20 percent in alcohol produced some irritation and sensitization (Table 7).

Propyl Gallate, as a 10 percent solution in propylene glycol, was applied to the skin of the back of the hand of each of 2 subjects for 24 hours. No skin irritation was observed<sup>(10)</sup> (Table 7).

Propyl Gallate, 20 percent 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 2 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 percent Propyl Gallate to 2 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. Propyl Gallate was a contact sensitizer at high concentrations (10 percent). However, human tolerance to low Propyl Gallate concentrations may be the result of repeated oral exposures to low doses of Propyl Gallate in food<sup>(146)</sup> (Table 7).

A repeat insult patch test (RIPT) on a total of 16 subjects was conducted using a lipstick formulation containing less than 1 percent Propyl Gallate. The test material "sufficient to cover a Webril pad" was applied at 48- and/or 72-hour intervals to the upper arms and covered for the first 24 hours between applications. Each site was scored at 48 and/or 72 hours when new patches were applied. The 22-day induction period was followed by a 12-day rest period before application of a 24-hour occlusive challenge patch. No irritation was observed in the 15 subjects who completed the test program, but 1 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"<sup>(162)</sup> (Table 7).

Two lipstick formulations, each containing 0.005 percent Propyl Gallate, were tested for cumulative irritancy using 14 subjects, of which 12 completed the test. Approximately 0.2 g of each lipstick and 0.3 ml of 2 reference materials (of low and high irritancy) were applied daily by occlusive patch to the back of each panelist. Patches were removed after 23 hours and scored 1 hour later, and the procedure was repeated for 21 consecutive days. The total calculated scores of the 2 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<sup>(161)</sup> (Table 7).

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.<sup>(163-165)</sup> Each preparation contained 0.003 percent Propyl Gallate. Topical, occlusive patches were applied to the upper backs of the panelists on Monday, Wednesday, and Friday for 3 consecutive weeks. 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-hour challenge patches were then applied to adjacent sites and scored at 48 and 96 hours. The suntan oil, tested on 151 subjects, produced 8 scores of 1 and 2 scores of 2 on induction and no positive reactions on challenge. The suntan cream and sun pro-

TABLE 7. Clinical Irritation and Sensitization of Propyl Gallate

| Compound Tested  | Type of Test   | No. of Humans | Results/Comments  | Reference |
|--|--|---------------|---|-----------|
| Propyl Gallate—10 percent solution in propylene glycol | Irritation—Applied to skin on back of hands for 24 hours       | 2             | No skin irritation  | 10        |
| Propyl Gallate—20 percent solution in alcohol          | Irritation/sensitization—Applied to forearms daily for 24 days | 10            | 3 exhibited mild reactions; 2 developed skin eruptions, were retested with 2 percent Propyl Gallate, and reacted mildly; authors concluded that Propyl Gallate was a contact sensitizer at high concentrations (10 percent) | 146       |
| Propyl Gallate—0.005 percent in a lipstick             | Cumulative irritancy   | 12            | Score of 1.67 (max = 630); essentially nonirritating  | 161       |
| Propyl Gallate—0.005 percent in a lipstick             | Cumulative irritancy   | 12            | Score of 29.51 (max = 630); essentially nonirritating   | 161       |
| Propyl Gallate—<1 percent in a lipstick                | RIPT*  | 15            | No irritation; 1 mild sensitization on challenge; did "not suggest significant dermatotoxicity"   | 162       |
| Propyl Gallate—0.003 percent in a suntan oil           | RIPT   | 151           | 8 scores of 1 (max = 4) and 2 scores of 2 on induction; no reactions on challenge; no significant allergic reactions  | 163       |
| Propyl Gallate—0.003 percent in a suntan butter        | RIPT   | 150           | No reactions; no instance of sensitization  | 164       |
| Propyl Gallate—0.003 percent in a sun protection stick | RIPT   | 154           | No reactions; no instance of sensitization  | 165       |
| Propyl Gallate—0.003 percent in a sunscreen            | RIPT   | 52            | Slight transient reactions; no irritation or sensitization  | 166       |
| Propyl Gallate—0.003 percent in a sunscreen            | RIPT   | 52            | Slight transient reactions; no irritation or sensitization  | 167       |
| Propyl Gallate—0.003 percent in a sunscreen            | RIPT   | 54            | Slight transient reactions; no irritation or sensitization  | 168       |
| Propyl Gallate—0.003 percent in a sunscreen            | RIPT   | 54            | Slight transient reactions; no irritation or sensitization  | 169       |
| Propyl Gallate—0.003 percent in a sunscreen            | RIPT   | 54            | Slight transient reactions; no irritation or sensitization  | 170       |
| Propyl Gallate—0.003 percent 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  | 171       |
| Propyl Gallate—0.003 percent in a cosmetic formulation | RIPT   | 54            | Slight transient reactions; no irritation or sensitization  | 172       |

\*RIPT, Repeat Insult Patch Test.

tection stick produced no reactions when tested on 150 and 154 subjects, respectively. The investigators in all three studies observed no instances of sensitization (Table 7).

Seven cosmetic formulations, including five sunscreens, were tested by RIPT for irritation and sensitization in 52 or 54 subjects (Table 7). Each formulation contained 0.003 percent Propyl Gallate. Occlusive patches containing 0.2 g samples of each product were applied for 24 hours to the volar arm or the back of each subject. Patches were then removed, and sites were scored on a scale of 0 to 4. This procedure was repeated 24 hours later, 3 times a week for 10 applications. After an 11- to 20-day rest, a challenge patch was applied to an adjacent site for 24 hours, and the area was scored upon removal and 24 hours later. Six of the formulations, including all five sunscreens, produced only slight transient reactions; the seventh likewise produced slight transient reactions but for one score of 2 on the second induction patch. No subsequent reactions were observed. All investigators found the formulations produced no irritation or sensitization<sup>(166-172)</sup> (Table 7)

### Photosensitivity/Phototoxicity

Propyl Gallate at 10 percent in alcohol was nonphotosensitizing to human skin. Cosmetic formulations containing 0.003 percent Propyl Gallate were essentially nonphotosensitizing and nonphototoxic in 17 tests using 371 subjects (Table 8).

Propyl Gallate, 10 percent in alcohol, was applied to the arms of 25 white subjects. When the sites dried, they were exposed to an FS-40 Westinghouse sunlamp (280 to 370 nm) at a dose of three times the individual's minimal erythema dose (MED). Erythema was evaluated 24 hours later. Propyl Gallate was then re-applied to the same site, allowed to dry, rinsed with warm water for 5 minutes, and radiated. Sites were evaluated 24 hours later. No contact sensitization, photosensitization, or primary irritation to Propyl Gallate was observed. Propyl Gallate was the most effective compound tested (due to the prevention of peroxide formation) for protection against UV light-induced erythema, and retained its effectiveness even after washing<sup>(173)</sup> (Table 8).

The photocontact sensitization of a sun protection stick containing 0.003 percent Propyl Gallate was evaluated using 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 48 hours for 5 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 hours. No reactions were observed. The sun protection stick was not a photosensitizer under the test conditions<sup>(174)</sup> (Table 8)

Seven cosmetic formulations, including five sunscreens, were tested for photosensitization in 26 to 28 subjects (Table 8). Each formulation contained 0.003 percent Propyl Gallate. Occlusive patches containing 0.2 g of each product were applied to the volar arms of the subjects for 24 hours. 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 minutes, resulting in a

TABLE 8. Clinical Photosensitivity/Phototoxicity of Propyl Gallate

| Compound Tested  | Type of Test               | No. of Humans | Results/Comments  | Reference |
|--|----------------------------|---------------|---|-----------|
| Propyl Gallate—10 percent solution in alcohol          | Photosensitization         | 25            | No contact sensitization, photosensitization, or primary irritation observed; effective compound for protection against UV light-induced erythema | 173       |
| Propyl Gallate—0.003 percent in a sun protection stick | Photocontact sensitization | 25            | No reactions; not a photosensitizer under test conditions   | 174       |
| Propyl Gallate—0.003 percent in a sunscreen            | Photosensitization (UVA)   | 26            | Slight transient reactions; no photosensitization   | 166       |
| Propyl Gallate—0.003 percent in a sunscreen            | Photosensitization (UVA)   | 26            | Slight transient reactions; no photosensitization   | 167       |
| Propyl Gallate—0.003 percent in a sunscreen            | Photosensitization (UVA)   | 28            | Slight transient reactions; no photosensitization   | 168       |
| Propyl Gallate—0.003 percent in a sunscreen            | Photosensitization (UVA)   | 28            | Slight transient reactions; no photosensitization   | 169       |
| Propyl Gallate—0.003 percent in a sunscreen            | Photosensitization (UVA)   | 28            | Slight transient reactions; no photosensitization   | 170       |
| Propyl Gallate—0.003 percent in a cosmetic formulation | Photosensitization (UVA)   | 26            | Slight transient reactions; no photosensitization   | 172       |
| Propyl Gallate—0.003 percent in a cosmetic formulation | Photosensitization (UVA)   | 26            | Slight transient reactions but for a score of 2 (max = 4) on 2nd induction patch; no subsequent reactions observed; no photosensitization         | 171       |
| Propyl Gallate—0.003 percent in a sunscreen            | Phototoxicity (UVA)        | 10            | Slight transient reactions; no phototoxicity  | 166       |
| Propyl Gallate—0.003 percent in a sunscreen            | Phototoxicity (UVA)        | 10            | Slight transient reactions; no phototoxicity  | 167       |
| Propyl Gallate—0.003 percent in a sunscreen            | Phototoxicity (UVA)        | 10            | No reactions; no phototoxicity  | 168       |
| Propyl Gallate—0.003 percent in a sunscreen            | Phototoxicity (UVA)        | 10            | No reactions; no phototoxicity  | 169       |
| Propyl Gallate—0.003 percent in a sunscreen            | Phototoxicity (UVA)        | 10            | No reactions; no phototoxicity  | 170       |
| Propyl Gallate—0.003 percent in a cosmetic formulation | Phototoxicity (UVA)        | 10            | Slight transient reactions; no phototoxicity  | 171       |
| Propyl Gallate—0.003 percent in a cosmetic formulation | Phototoxicity (UVA)        | 10            | No reactions; no phototoxicity  | 172       |
| Propyl Gallate—0.003 percent in a sun protection stick | Phototoxicity (UVA)        | 10            | No reactions; not phototoxic under test conditions  | 175       |
| Propyl Gallate—0.003 percent in a suntan oil           | Controlled use             | 78            | No clinically significant reactions observed; safe for intended use   | 176       |



total UVA dosage of 4,400  $\mu\text{W}/\text{cm}^2$ ; the other forearm served as the nonradiated control. This procedure was repeated 3 times per week for 10 applications/radiations. After an 11- to 20-day rest, adjacent sites were challenged with a 24-hour patch application followed by radiation. These sites were scored 24 and 48 hours later. Six of the formulations produced only slight transient erythematous 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<sup>(166-172)</sup> (Table 8).

Each of these 7 formulations was also tested for phototoxicity in 10 subjects (Table 8). Occlusive patches containing 0.2 g samples of each product were applied to the scrubbed, tape-stripped volar arms for 24 hours. Sites were scored on patch removal, and one arm of each subject was then irradiated with UVA light for 15 minutes for a total dose of 4,400  $\mu\text{W}/\text{cm}^2$ . Sites were scored again immediately following, 24 and 72 hours, 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.<sup>(166-172)</sup>

The phototoxicity of a sun protection stick containing 0.003 percent Propyl Gallate was evaluated using 10 subjects. Applications of 5 ml/cm<sup>2</sup> of the sun stick were rubbed into the lower back of each subject and then occluded for 24 hours. Patches were removed, and the sites were radiated for 20 minutes with filtered long-wave UV light (UVA 30 mW/cm<sup>2</sup>) using a 150W xenon solar simulator (emission of 124 mW/cm<sup>2</sup>). Adjacent skin sites received similar treatment as controls. Reactions were graded 24 and 48 hours later. No reactions were observed; the investigators concluded that the sun protection stick was not phototoxic under the test conditions<sup>(175)</sup> (Table 8).

A suntan oil containing 0.003 percent 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 minute intervals for 2 hours of continuous sun exposure (11:30 am to 1:30 pm). Subjects were required to enter the pool for 10 minutes at the end of each hour. These procedures were repeated the second day. Any reactions immediately, 24, or 48 hours after application were noted. No clinically significant reactions were observed; the product was considered safe for intended use<sup>(176)</sup> (Table 8).

### Oral Toxicity

A man 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.<sup>(10)</sup>

Nine infants in a pediatric ward of a hospital were 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 hours. The preservative was identified as a mixture of BHA, BHT, and Propyl Gallate. In addition, age was an important factor in respect to the toxicity of phenolic compounds, since 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.<sup>(177)</sup>

### 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 when heated or in mild alkaline environments.

In cosmetics, Propyl Gallate is employed 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. According to the industry's voluntary submissions to the FDA in 1981, Propyl Gallate alone is used in over 118 cosmetic products at concentrations up to 5 percent. Most of these formulations, however, contain less than 0.1 percent Propyl Gallate. Available test information indicates that much lower concentrations are actually used.

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 used in food at concentrations of 0.01484 to 0.00001 percent and is restricted to 0.2 percent of the fat or oil content of the food. The average daily intake of this ingredient from food has been estimated to be 0.014 mg/kg (ages 0 to 5 months), 0.114 mg/kg (ages 6 to 11 months), 0.135 mg/kg (ages 12 to 23 months), and 0.065 mg/kg (ages 2 to 65+ years). The acceptable daily intake of Propyl Gallate for man according to FAO/WHO is 0.2 mg/kg (unconditional) or 0.2 to 0.5 mg/kg (conditional). Additionally, Propyl Gallate is approved for use as a direct food additive in 12 European countries, as well as Canada, Australia, South Africa, and Russia at concentrations up to 2.0 percent.

Propyl Gallate has numerous biological effects. Many of these are 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/antitumorigenesis, anticancer, antiteratogenesis, and anticariogenesis.

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

Acute animal toxicity studies indicate that Propyl Gallate is slightly toxic when ingested and practically nontoxic when applied to the skin. Findings in subchronic studies include: 20 percent 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 percent or doses up to 500 mg/kg. Propyl Gallate is a strong sensitizer when tested intradermally, less sensitizing when

tested topically, and almost nonsensitizing topically at 0.1 percent following ingestion of 10 percent Propyl Gallate for 1 week. Acute eye irritation tests conducted on 9 cosmetic formulations, each containing less than 1 percent Propyl Gallate, were negative.

Numerous chronic oral toxicity studies indicate that Propyl Gallate, when ingested at concentrations up to 5 percent in the diet for up to 2 years, is practically nontoxic to rats, mice, dogs, and guinea pigs.

A phototoxicity study conducted on a cosmetic formulation containing 0.003 percent Propyl Gallate determined that the product was not phototoxic to guinea pigs.

Results of Ames tests, chromosomal aberration assays, cytogenetic assays, dominant lethal assays, and host-mediated assays indicated that Propyl Gallate was nonmutagenic both with and without metabolic activation, except for one chromosomal aberration assay. Propyl Gallate enhanced the mutagenic activity of N-hydroxy-2-acetylaminofluorene and 4-nitroquinoline-1-oxide in an Ames test using *S. typhimurium* strains TA98 and TA100, respectively. Metabolic activation was required for this to occur.

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. In a recently completed bioassay, the National Toxicology Program reported that Propyl Gallate was noncarcinogenic in mice and rats, although an increased incidence of malignant lymphomas in male mice may have been related to the administration of Propyl Gallate.

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.

Clinical studies indicate Propyl Gallate to be nonirritating at concentrations up to 10 percent; however, it is sensitizing at this and higher concentrations. Cumulative irritancy andRIPTs conducted on cosmetic formulations containing less than 1 percent Propyl Gallate produced no significant signs of irritation or sensitization in a total of 868 subjects. Propyl Gallate at a concentration of 10 percent in alcohol was nonphototoxic in 25 subjects. Cosmetic formulations, each containing 0.003 percent Propyl Gallate, produced no signs of photosensitization or phototoxicity in a total of 371 subjects. Repeated oral ingestion of 0.5 g Propyl Gallate did not result in toxicity.

## DISCUSSION

The Panel, in review of Propyl Gallate, notes the excellent clinical margin of safety if the concentration in cosmetics does not exceed 1 percent. After intradermal induction in guinea pigs with 5 percent Propyl Gallate, patch testing produced sensitization at 0.5 and 2 percent but not at 0.1 percent. Human studies showed significant induction of sensitization at concentrations exceeding 10 percent Propyl Gallate. Furthermore, Propyl Gallate, as an antioxidant in cosmetics, is used predominantly at concentrations not exceeding 0.1 percent. Thus, the Panel agrees that a safe concentration for the use of Propyl Gallate in cosmetics should not exceed 1 percent.

## CONCLUSION

On the basis of the available information, the Panel concludes that Propyl Gallate is safe as a cosmetic ingredient at concentrations not exceeding 1 per cent.

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