Safety Assessment of Propyl Gallate as Used in Cosmetics

Status:	Re-Review for Panel Consideration
Release Date:	May 10, 2024
Panel Meeting Date:	June 3 – 4, 2024

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume. This safety assessment was prepared by Preethi Raj, M.Sc., Senior Scientific Analyst/Writer, CIR.

© Cosmetic Ingredient Review
1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651
cirinfo@cir-safety.org

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc.,
Senior Scientific Analyst/Writer, CIR
Date: May 10, 2024
Subject: Re-Review of the Safety Assessment of Propyl Gallate as Used in Cosmetics

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a review of the safety of Propyl Gallate in 1985 (identified in the pdf as *originalreport_PropylGallate_062024*). The Panel concluded, on the basis of the available information presented in the report, that Propyl Gallate was safe as a cosmetic ingredient at concentrations not exceeding 1%. The Panel decided to reopen this report d in November 2003 to consider the sensitization potential of Propyl Gallate (as seen in patch testing results) at lower concentrations than originally thought (i.e., at concentrations less than 1%). Based on the data evaluated during the re-review process, the Panel concluded that Propyl Gallate is safe in the practices of use described in the amended safety assessment at concentrations less than or equal to 0.1%, as published in 2007 in a Final Amended Report(*amendedreport2007_PropylGallate_062024*).

Because it has been at least 15 years since the previous re-review was published, in accordance with Cosmetic Ingredient Review (CIR) Procedures, the Panel should consider whether the safety assessment of Propyl Gallate should be re-opened. In April 2024, an extensive search of the world's literature was performed or studies dated 2002 forward. An historical overview, comparison of original and new use data, and the search strategy used are included herein (*newdata_PropylGallate_062024*).

Newly found studies include updated regulatory limits for human and animal consumption, in vitro genotoxicity studies, in vitro developmental and reproductive toxicity studies, studies on estrogenic and in vitro effects on tumor cells, an in vitro dermal irritation study, ocular irritation studies, and numerous clinical patch test reports. Of note, data on in vitro developmental and reproductive toxicity as well as developmental toxicity in zebrafish were not present in the amended safety assessment. Also, in vitro ocular irritation data and an ocular irritation study with positive results were found.

Also included for your review is a table of current and historical use data (*usetable_PropylGallate_062024*). According to 2023 FDA VCRP data, Propyl Gallate had 86 reported uses; in 2002, 164 uses were reported. In 2023, the maximum reported concentration of use for Propyl Gallate was at up to 0.012% in eyeliners, compared to at up to 0.1% in other personal cleanliness products, as reported in 2003. Reported uses and concentrations of use have decreased significantly. No new product categories are reported to be in use.

If upon review of the new studies and the updated use data the Panel determines that a re-review is warranted, a Draft Amended Report will be presented at an upcoming meeting.

Re-Review - Propyl Gallate - History and New Data

(Preethi Raj – June 2024 meeting)

Ingredients (1)	Citation	Conclusion	Use - New Data	Results	Use - Existing Data	Results	Notes
Propyl Gallate *Changes to Original List* none	JACT 4(3):23-64, 1985 IJT 26(S3):89-118, 2007	safe at < 1% safe at ≤ 0.1%	frequency of use (2023) conc of use (2023)	86 uses ≤ 0.012%	frequency of use (2002) conc of use (2003)	164 uses ≤ 0.1%	frequency of use has decreased significantly concentration of use has decreased slightly; no new use categories

NOTABLE NEW DATA			
Publication	**Study Type**	**Results – Brief Overview**	**Different from Existing Data?**
Non-Cosmetic Use			
https://www.ecfr.gov/	Regulation, use types	• 21CFR166.100: is listed as an optional preservative in margarine, at 0.0075% • 21CFR172.615: is listed as an authorized food additive for use in chewing gum base (not to exceed 0.1% alone or in combination) • 21CFR319.700: is listed as an antioxidant permitted for use in margarine or oleomargarine (0.02% maximum percent by weight, alone or in combination with other antioxidants) • 21CFR42.21: is listed as an approved preservative to make sausage (0.003% based on total weight, 0.006% in combination with other anti-oxidants for use in meat) • 21CFR175.300: is listed as an antioxidant used in resinous and polymeric food-contact surfaces (such as in metal cans)	Yes, these CFRs are not in the original report
https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm	Approved inactive ingredient uses	Propyl Gallate has approved uses in an oral concentrate at 0.2 mg/ml, in a topical gel at 0.05% w/w, and at up to 7 mg in a tablet form	Yes, no mention of use as an inactive ingredient
EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS). Scientific opinion on the re-evaluation of propyl gallate (E 310) as a food additive. *EFSA J.* 2014; 12(4): 3642.	Regulation, food additive	Based on a NOAEL of 135 mg/kg bw/d from a 90-d study in rats, and taking account of the Scientific Committee of EFSA Opinion on default values, the Panel derived an ADI of 0.5 mg/kg bw/d for Propyl Gallate.	Yes, ADI value has been updated (previously 0.2 – 0.5 mg/kg)
EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). Safety and efficacy of propyl gallate for all animal species. *EFSA J.* 2020; 18(4): 6069.	Regulation, animal feed	Propyl Gallate is safe in animal feed at the following doses: • 40 mg/kg, for veal calves, cattle for fattening, dairy cows, sheep, goats, sows, horses and salmonids • 100 mg/kg, for ornamental fish • 15 mg/kg complete feed for chickens for fattening; 20 mg/kg complete feed for turkeys for fattening and laying hens and rabbits; 27 mg/kg complete feed for piglets and pigs for fattening, and 71 mg/kg complete feed for dogs. The Panel could not conclude on a safe level for cats.	Yes, safe doses for use in animal feed are not provided in the report
EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). Safety of a feed additive consisting of propyl gallate for all animal species (FEFANA ABL). *EFSA J.* 2024; 22: 1-11	Regulation, animal feed	Based on the results of a tolerance study, the EFSA Panel concluded that Propyl Gallate at a maximum concentration of 71 mg/kg complete feed is safe for cats. The use of Propyl Gallate in animal nutrition at the concentrations in complete feed was also considered safe and was not a concern for consumer safety.	Yes, safe doses for use in animal feed are not provided in the report

NOTABLE NEW DATA			
Publication	**Study Type**	**Results – Brief Overview**	**Different from Existing Data?**
Toxicological Studies			
https://chem.echa.europa.eu/100.004.090/dossier-view/41257f7c-4905-48ba-a2ed-daa98261056d/0db5421d-13c1-44cd-9d8f-915b6e76edcc_0db5421d-13c1-44cd-9d8f-915b6e76edcc?searchText=121-79-9	Acute toxicity, dermal	OECD TG 402. Male and female Wistar rats (5/sex); 2000 mg/kg bw Propyl Gallate, in water; a 24-h, semi-occlusive application was made to 10% of the total body surface area. The dermal LD_{50} value was determined to be > 2000 mg/kg bw.	No acute dermal exposure in original report
Developmental and Reproductive Toxicity			
Yang et al. High-dose synthetic phenolic antioxidant propyl gallate impairs mouse oocyte meiotic maturation through inducing mitochondrial dysfunction and DNA damage. *Environ Toxicol*. 2023; 38: 1800-1810.	Reproductive toxicity, in vitro	Female Kunming mice were injected with pregnant mare serum gonadotropin and were killed after 48 h. Extracted oocytes were maintained at the germinal vesicle stage in medium. Oocytes were treated with 0, 150, 200 or 250 µM Propyl Gallate, in DMSO, for 12 h; negative controls were untreated. There was a statistically significant reduction of polar body extrusion in oocytes treated with 200 µM Propyl Gallate compared to the negative control and oocytes treated with 150 µM Propyl Gallate. In subsequent experiments, cells treated with 200 µM Propyl Gallate showed statistically significant increases in disturbed spindle organization, chromosome misalignment, mitochondrial dysfunction, apoptosis, and DNA damage, compared to controls.	Yes, there is no data on in vitro reproductive toxicity in the original report
Yang et al. Propyl gallate exposure affects the mouse 2-cell stage embryoinic development through inducing oxidative stress and autophagy. *Food Chem Toxicol*. 2024; 114488.	Developmental toxicity, in vitro	Fertilized embryos collected from ICR female mice were treated with 0, 25, 50, or 75 µM Propyl Gallate, dissolved in DMSO (≤ 1%), and were cultured for 24 h. Control embryos were untreated. A statistically significant reduction in 2-cell stage embryos was observed after treatment with 50 µM and 75 µM Propyl Gallate, compared to controls, but there were no remarkable differences in developmental competence in the 25 µM group. ROS, DNA damage, autophagy, rate of abnormal mitochondria distribution, and epigenetic modification of mouse 2-cell stage embryos were evaluated in embryos treated with only 50 µM; a statistically significant increase was seen for all of these measures in treated embryos, compared to controls.	Yes, there is no data on in vitro developmental toxicity in the original report

NOTABLE NEW DATA			
Publication	**Study Type**	**Results – Brief Overview**	**Different from Existing Data?**
Baran et al. Determination of developmental toxicity of zebrafish exposed to propyl gallate dosed lower than ADI (acceptable daily intake). *Reg Toxicol Pharm*. 2018; 94: 16-21.	Developmental toxicity, in vivo	The potential effects of injected Propyl Gallate on body abnormalities, hatching, survival rates, and accumulation of ROS and apoptosis were evaluated in zebrafish embryos. AB strain zebrafish embryos (n = 200 ± 5 embryos/group) had 5 nl of approximately 1, 10, or 50 ppm Propyl Gallate injected into the yolk sac of fertilized embryos and were cultured in medium for 96 h. Two control groups which were either injected with 5 nl water or that were not injected were used; 3 replicates for each group were used. No statistically significant differences were observed in the survival rate, between treated groups and controls. Propyl Gallate exhibited a statistically significant accelerating effect on hatching rate in the 1 and 10 ppm treated groups and at 24 h post-fertilization. No statistically significant differences in body abnormalities were observed between the 1 ppm Propyl Gallate group and controls; statistically significant differences in pericardial edema, yolk sac edema, and spinal curvature were observed in the 10 ppm and 50 ppm groups, when compared to controls. Pericardial edema observed in the 50 ppm group was the most serious malformation. Cell death increased in a statistically significant and dose-dependent manner; a dramatic increase in ROS and apoptotic cells were identified in embryos treated with the highest concentration of Propyl Gallate.	Yes, there is no data on developmental toxicity using zebrafish in the original report
Genotoxicity Studies			
Tayama et al. Cytogenetic effects of propyl gallate in CHO-K1 cells. *Mut Res*. 2001; 498: 117-127.	Genotoxicity, in vitro	An increase in sister chromatid exchanges, chromosomal aberrations, and endoreduplication occurred in CHO-K1 cells treated with 0.25 – 1.5 mM Propyl Gallate, in the presence and absence of metabolic activation.	no
Sasaki et al. The comet assay with 8 mouse organs: results with 39 currently used food additives. *Mut Res*. 2002; 519: 103-119.	Genotoxicity, in vivo	Comet assay. Male ddY mice (n =4) were orally dosed with a single dose of up to 2000 mg/kg Propyl Gallate and were killed after 3 or 24 h after exposure. The glandular stomach, colon, liver, kidney, urinary bladder, lung, brain, and bone marrow were removed and underwent histopathological and other analyses to assess toxic effects. No death, morbidity, or clinical signs were observed after treatment. Propyl Gallate did not increase DNA damage in any of the studied organs and no treatment-related effects were observed.	no
Hamishekhar et al. Geno- and cytotoxicity of propyl gallate food additive. *Drug Chem Toxicol*. 2014; 37(3): 241-246.	Genotoxicity, in vitro	Comet assay. A549 lung carcinoma cells were treated with 0, 0.0001, 0.0002, 0.0005, 0.0008, or 0.001 M Propyl Gallate, in RPMI-1640 media/DMSO for up to 72 h. Hydrogen peroxide was used for positive controls. Statistically significant increases in DNA strand breaks and cells in the early stage of apoptosis (more than 68% of treated cells) were observed in cells treated with Propyl Gallate compared to controls. In an MTT assay, dose- and time-dependent reduction of cell growth was observed with an IC_{50} of approximately 0.001 M Propyl Gallate at 48 h and 0.0005 M Propyl Gallate at 72 h.	no

NOTABLE NEW DATA			
Publication	**Study Type**	**Results – Brief Overview**	**Different from Existing Data?**
Carcinogenicity Studies			
Park, Woo Hyun. Propyl gallate reduces the growth of lung cancer cells through caspase-dependent apoptosis and G1 phase arrest of the cell cycle. *Onc Rep*. 2020; 44: 2783-2791.	In Vitro Cell Transformation	Propyl Gallate inhibited the growth of both Calu-6 and A549 lung cancer cells (tested at up to 1600 µM) in a dose-dependent manner with an IC_{50} of 800 µM at 24 h based on MTT assays. Treatment with Propyl Gallate also inhibited the growth of Calu-6 cells via caspase-dependent apoptosis and caused G_1 phase arrest of the cell cycle.	no
Park, Woo Hyun. Propyl gallate induces human pulmonary fibroblast cell death through the regulation of Bax and caspase-3. *Ann Med*. 2024; 56 (1): 1-12.	In Vitro Cell Transformation	Human pulmonary fibroblast cells were treated with 100 – 1600 µM Propyl Gallate for 24 h. Ethanol (0.2%) and DMSO (0.3%) were used as vehicle controls. Propyl Gallate (1600 µM) slightly increased the number of sub-G1 cells and resulted in the initiation of cell death along with a loss of mitochondrial membrane potential.	no
Park, Woo Hyun. Propyl gallate induces cell death in human pulmonary fibroblast through increasing reactive oxygen species levels and depleting glutathione. *Nature*. 2024; 14: 5375.	In Vitro Cell Transformation	Propyl Gallate exhibited an anti-growth effect on human pulmonary fibroblast cells. Propyl Gallate (100 – 800 µM) increased the levels of total ROS at early time points of 30 – 180 min and 24 h; 100 -800 µM increased GSH-depleted cell number at 24 h and reduced GHS levels at 30-180 min. Additionally, Propyl Gallate downregulated the activity of superoxide dismutase and upregulated the activity of catalase in human pulmonary fibroblast cells. Treatment with 800 µM Propyl Gallate increased the number of apoptotic cells and cells that lost mitochondrial membrane potential.	no
Other Relevant Studies			
Amadasi et al. Identification of xenoestrogens in food additives by an integrated in silico and in vitro approach. *Chem Res Toxicol*. 2009; 22(1): 52-63.	Estrogenic activity, in vitro	The estrogen antagonist activity of Propyl Gallate was evaluated in a transactivation assay. MCF-7 cell lines, transfected with the luciferase gene, were treated with 10 and 100 nM Propyl Gallate, in triplicates. 17β-estradiol was used to treat controls. Propyl Gallate-treated cells were able to antagonize a 10-fold higher concentration of 17β-estradiol activity by 33 and 40%, respectively.	Yes, there is no data on endocrine effects in the original report
Dermal Irritation			
https://chem.echa.europa.eu/100.004.090/dossier-view/41257f7c-4905-48ba-a2ed-daa98261056d/0db5421d-13c1-44cd-9d8f-915b6e76edcc_0db5421d-13c1-44cd-9d8f-915b6e76edcc?searchText=121-79-9	Skin irritation, in vitro	OECD TG 439. In vitro skin irritation: reconstructed human epidermis test method. 10 mg undiluted Propyl Gallate was applied to 3 replicate tissue models and cell viability was measured in an MTT assay. Appropriate positive and negative controls were used. After a 15-min exposure and 42 h post-incubation period the mean relative tissue viability for treated tissue was 70.3%. Propyl Gallate was considered non-irritating.	no
Ocular Irritation			
https://chem.echa.europa.eu/100.004.090/dossier-view/41257f7c-4905-48ba-a2ed-daa98261056d/0db5421d-13c1-44cd-9d8f-915b6e76edcc_0db5421d-13c1-44cd-9d8f-915b6e76edcc?searchText=121-79-9	Ocular irritation, in vitro	OECD TG 437. Bovine corneal opacity and permeability assay. All 3 corneas treated with 750 µl Propyl Gallate (20% suspension, in saline) showed uniform milky opacity of the tissue; the mean (triplicate) in vitro irritation score was 29.65. Appropriate positive and negative controls were used. No prediction regarding the classification of Propyl Gallate was possible based on this mean in vitro irritation score.	Yes, in vitro ocular irritation data is not in the original report

NOTABLE NEW DATA			
Publication	**Study Type**	**Results – Brief Overview**	**Different from Existing Data?**
https://chem.echa.europa.eu/100.004.090/dossier-view/41257f7c-4905-48ba-a2ed-daa98261056d/0db5421d-13c1-44cd-9d8f-915b6e76edcc_0db5421d-13c1-44cd-9d8f-915b6e76edcc?searchText=121-79-9	Ocular irritation, animal	OECD TG 405. Acute eye/irritation/corrosion. 0.1 g of Propyl Gallate was applied, neat, to the eye of 1 New Zealand white rabbit for 1 h. The untreated eye served as the control. The treated eye was rinsed with saline and was observed for up to 72 h. Draize irritation scores were obtained after 1, 24, 48, and 72 h. Under the conditions of the study, conjunctival redness, chemosis, hypersecretion, corneal effects, and iris lesions (iridial response grade 2 for 72 h) were observed. These effects were not reversible; Propyl Gallate was considered a severe ocular irritant.	Yes, ocular irritation study results in the original report are negative
CLINICAL STUDIES			
Retrospective Studies			
Garcia-Melgares et al. Sensitization to gallates: review of 46 cases. *Actas Derm*. 2007; 98: 688-693.	Clinical group patch test, retrospective study	Propyl Gallate was applied at a concentration of 1% in petrolatum as part of a preservative and bakery series, in a patch test using 1173 patients. There were 30 positive patch test results for Propyl Gallate. Sensitization attributed to cosmetics was mainly due to cheilitis, resulting from the use of Propyl Gallate in lipsticks.	no
Gamboni et al. Allergic contact stomatitis to dodecyl gallate? A review of the relevance of positive patch test results to gallates. *Aust J Dermatol*. 2013; 54: 213 – 217.	Clinical group patch test, retrospective study	Propyl Gallate was patch tested at 1% (in petrolatum) in 2773 subjects. Patch tests were read on day 2 and day 4. There were 46 positive patch reactions, 7 of which were definitely positive reactions and 39 which were uncertain. After review of the patients' likely source of Propyl Gallate exposure, 3/7 of the positive patch reactions resulted from a relevant product source and 4/7 of the reactions resulted from a possibly relevant product source.	no, but larger number of subjects tested
Perez et al. Positive rates to propyl gallate on patch testing: a change in trend. *Contact Point*. 2008; 58: 47-66.	Clinical group patch test, retrospective study	N= 9529 subjects were patch tested, from 1998 – 2005 (analyzed as 2 time periods: 1988-1996 and 1997-2005) to the face series. Propyl Gallate was tested at 1% in petrolatum; patch tests were read at day 2 and day 4. Positive reactions were scored as per ICDRG recommendations (+, ++, +++). A total of 55 patients had positive reactions to Propyl Gallate, 46 of these reactions were seen in females and 9 were seen in males. Using Chi-square analysis, there was a statistically significant difference in the positivity rates between the 1988-1996 period (0.45%) and the 1997-2005 period (0.77%).	no, but larger number of subjects tested
Case Reports			
Pandhi et al. Contact depigmentation induced by propyl gallate. *Clin Exper Dermatol*. 2010; 36: 366-368.	Case report, contact depigmentation	A 41-yr-old woman presented with depigmentation in the center of her forehead) and bilateral depigmented lesions on the dorsae of both feet. The subject reported using lipstick or liquid product in her hair parting and the use of rubber flip-flops on her feet. Patch testing was performed with the Indian standard and cosmetic series of allergens. Vesicles and ulceration were observed in response to testing with Propyl Gallate (+++); the standard patch test was extended to 14 d and irregular depigmentation was seen only at the Propyl Gallate test site. Partial re-pigmentation occurred after 6-mo treatment with topical mometasone furoate (0.01%) and tacrolimus (0.1%) ointment, and avoiding cosmetics containing Propyl Gallate and slippers made of plastic/rubber materials.	no

NOTABLE NEW DATA			
Publication	**Study Type**	**Results – Brief Overview**	**Different from Existing Data?**
Yu and Scheinman. Lip and periroral dermatitis caused by propyl gallate. *Dermatitis*. 2010; 21(2): 118-119.	Clinical patch test	A 30-yr-old Caucasian female presented with itchy and painful lip rash; erythema and scaling of the lips was observed. Allergic contact cheilitis was suspected. Patch testing was performed with a modified NACDG standard, preservative, fragrance, bakery, hair, and sunscreen series. After 72 h, several positive reactions were observed, including a ++ reaction to Propyl Gallate. Propyl Gallate was an ingredient in the patient's long used lip balm; the patient's lip dermatitis resolved after stopping use of the lip balm and avoiding foods likely to contain Propyl Gallate.	no
Ozkaya et al. Allergic contact cheilitis from a lipstick misdiagnosed as herpes labialis: subsequent worsening due to Zovirax contact allergy. *Aust J Dermatol*. 2007; 48: 190-192.	Clinical patch test	A 29-yr-old woman presented with allergic contact cheilitis (misdiagnosed as herpes labialis) which worsened with application of a herpes-treatment cream (which previously did not cause reactions). Occlusive patch testing was performed with various products from the same brand. The cream product, containing propylene glycol, and propylene glycol alone (+++) patch tested positive at the 96 h reading. Symptoms persisted after 2 wk, and resolved after application of 0.1% hydrocortisone-17-butyrate cream. Further patch testing was performed with a series of preservatives, emulsifying vehicles and fragrances, and the patient's own personal care products. Apart from nickel sulfate, the patient patch tested positive to a frequently used lipstick and Propyl Gallate. No lesions occurred after the patient discontinued use of the lipstick and any cosmetics or topical creams containing Propyl Gallate and propylene glycol in a 3-mo follow-up.	no
Holzer et al. A fishy situation: allergic contact dermatitis of the fingertips due to propyl gallate. *Dermatitis*. 2021; 32(2): e29-e34.	Clinical patch test	A patch test was performed using the American Contact Dermatitis Society Core series in a 58-yr-old woman with a 1-yr history of dermatitis localized to the first 3 fingertips of both hands. Positive reactions included a 2+ to Propyl Gallate (in 1% petrolatum). Upon review of her personal products, it was discovered that her fish food contained Propyl Gallate (amount not specified). She had begun to crush and sprinkle the fish food (using the thumb and her second and third fingers of both hands) roughly 1 yr prior to the onset of symptoms.	no
Foti et al. Allergic contact dermatitis to propyl gallate and pentylene glycol in an emollient cream. *Aust J Dermatol*. 2010; 51: 147-148.	Clinical patch test	A 62-yr-old man with a 20-yr history of seborrheic dermatitis presented with progressively worsening facial dermatitis after the use of an OTC cream containing hydrocortisone 17-butyrate, for 6 mo. Patch tests with the SIDAPA standard series and a corticosteroid series were performed. Results were interpreted according to ICDRG criteria. The patient had strong reactions (+++) to the corticosteroid mix. Patch testing with the OTC cream revealed a positive reaction (++) to the product at days 2 and 5. Subsequent testing with Propyl Gallate (1% in petrolatum) was positive; patch testing of butylene glycol was negative. Patch testing of pentylene glycol and propylene glycol was also positive, suggesting possible cross-reaction and/or sensitization to glycols.	no

NOTABLE NEW DATA			
Publication	**Study Type**	**Results – Brief Overview**	**Different from Existing Data?**
Occupational Exposure			
Mahendran et al. Allergic contact dermatitis from occupational propyl gallate exposure. *Contact Point*. 2002; 47(109): 122-123.	Occupational case report, patch test	A 41-yr-old man presented with marked erythema and edema around the eyes after working at a synthetic textile plant. A day prior to the reaction, he had been cleaning a premix hopper which had Propyl Gallate injected into it, in a powdered form. Upon being patch tested with the European standard series, and Propyl Gallate, the man experienced a positive reaction to 1% Propyl Gallate (in petrolatum) on days 2 and 4 and in ethanol on day 2. His symptoms resolved after redeployment away from Propyl Gallate exposure and with the use of oral antihistamines.	no

ADI – acceptable daily intake; DNA – deoxyribonucleic acid; EFSA- European Food Safety Authority; IC_{50} – half maximal inhibitory concentration; ICDRG- International Contact Dermatitis Research Group; DMSO – dimethyl sulfoxide; MTT – 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide; NACDG – North American Contact Dermatitis Group; OECD – Organisation for Economic Cooperation and Development; OTC – over-the counter; RPMI – Roswell Park Memorial Institute; ROS – reactive oxygen species; TG – test guideline

Search (from 2002 on)

Pubmed (General search was also performed)

((((((((((propyl gallate) OR (121-79-9)) OR (3,4,5-Trihydroxybenzoic Acid, Propyl Ester)) OR (Benzoic Acid, 3,4,5-Trihydroxy-, Propyl Ester)) OR (OriStar PG)) OR (Uantox PG)) OR (Photozomes Mix II g)) OR (Reconcyl)) OR (Sea Parsley)) OR (Sea Parsley G)) OR (Uantox 3)) OR (Unisooth EG-28)) AND (2002:2024[pdat]) – 7,559,558 hits/5 useful

AND toxicity – 309, 684 hits/ 3 useful

Frequency (2023/2002) and concentration (2023/2003) of use o according to likely duration and exposure and by product category

	# of Uses		*Max Conc of Use (%)*	
	2023[1]	**2002[2]**	**2023[3]**	**2003[2]**
Totals*	**86**	**164**	**0.00001 – 0.012**	**0.000005 – 0.1**
summarized by likely duration and exposure**				
Duration of Use				
Leave-On	*82*	*152*	*0.00008 – 0.012*	*0.000005 – 0.05*
Rinse-Off	*4*	*9*	*0.00001 – 0.00011*	*0.000005 – 0.1*
Diluted for (Bath) Use	*NR*	*3*	*NR*	*NR*
Exposure Type				
Eye Area	7	17	0.00016 – 0.012	0.01 – 0.03
Incidental Ingestion	51	75	0.0004	0.05
Incidental Inhalation-Spray	9[a]; 4[b]	1; 21[a]; 17[b]	NR	0.002 – 0.01; 0.000005 – 0.0002[b]
Incidental Inhalation-Powder	2; 4[b]	2; 17[b]	0.0022 – 0.0024[c]	0.05; 0.000005 – 0.0002[b]
Dermal Contact	34	84	0.00001 – 0.012	0.000005 – 0.1
Deodorant (underarm)	NR	NR	not spray: 0.00008	NR
Hair - Non-Coloring	NR	2	0.00004 – 0.00008	NR
Hair-Coloring	NR	NR	NR	NR
Nail	NR	1	NR	NR
Mucous Membrane	52	82	0.00001 – 0.0004	0.000005 – 0.1
Baby Products	NR	NR	NR	NR
as reported by product category				
Bath Preparations (diluted for use)				
Bath Oils, Tablets, and Salts	NR	3	NR	NR
Eye Makeup Preparations				
Eyebrow Pencil	NR	5	NR	NR
Eyeliner	NR	3	0.012	0.01
Eye Shadow	1	NR	NR	NR
Eye Lotion	NR	2	NR	NR
Mascara	1	2	0.00016	0.01
Other Eye Makeup Preparations	5	5	NR	0.03
Fragrance Preparations				
Cologne and Toilet Water	NR	NR	NR	0.003 – 0.01
Perfumes	NR	NR	NR	0.002
Powders (dusting/talcum, excl aftershave talc)	NR	1	NR	NR
Other Fragrance Preparation	NR	1	NR	NR
Hair Preparations (non-coloring)				
Hair Conditioner	NR	1	0.00008	NR
Shampoos (non-coloring)	NR	NR	0.00004	NR
Tonics, Dressings, and Other Hair Grooming Aids	NR	1	NR	NR
Makeup Preparations				
Blushers (all types)	NR	3	NR	NR
Face Powders	2	1	NR	0.05
Foundations	NR	2	NR	NR
Lipstick	51	75	0.0004	0.05
Makeup Bases	2	NR	NR	NR
Rouges	1	NR	NR	NR
Other Makeup Preparations	5	6	NR	0.05
Manicuring Preparations (Nail)				
Cuticle Softeners	NR	1	NR	NR
Personal Cleanliness Products				
Bath Soaps and Detergents	1	2	0.00001 – 0.00011	0.000005 – 0.002
Deodorants (underarm)	NR	NR	not spray: 0.00008	NR
Other Personal Cleanliness Products	NR	2	NR	0.1
Shaving Preparations				
Aftershave Lotion	NR	NR	NR	0.0004
Skin Care Preparations				
Cleansing	1	4	NR	NR
Face and Neck (exc shave)	4	5	not spray: 0.0022	NR
Body and Hand (exc shave)	NR	12	not spray: 0.0024	0.0002
Foot Powders and Sprays	NR	NR	NR	0.000005
Moisturizing	NR	7	not spray: 0.00055 – 0.004	NR
Night	9	4	NR	NR
Paste Masks (mud packs)	2	NR	NR	NR
Skin Fresheners	NR	2	NR	NR
Other Skin Care Preparations	1	7	NR	NR
Suntan Preparations				
Suntan Gels, Creams, and Liquids	NR	3	not spray: 0.00008	NR
Indoor Tanning Preparations	NR	4	NR	NR

NR – not reported
*Because this ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
**likely duration and exposure are derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

REFERENCES

1. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. College Park, MD. 2023. (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2023; received February 2, 2023.)

2. Andersen FA (ed). Final report on the amended safety assessment of Propyl Gallate. *Int J Toxicol.* 2007;26 Suppl 3:89-118.

3. Personal Care Products Council. 2023. Concentration of Use by FDA Product Category: Propyl Gallate. (Unpublished data submitted by the Personal Care Products Council on February 22, 2023.)

Distributed for Comment Only -- Do Not Cite or Quote

JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 4, Number 3, 1985
Mary Ann Liebert, Inc., Publishers

2

Final Report on the Safety Assessment of Propyl Gallate

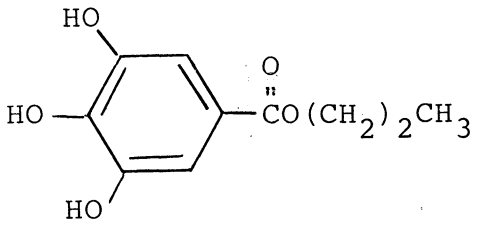
Propyl Gallate acid is used as an antioxidant in cosmetic products at concentrations normally less than 0.1 percent. Propyl Gallate is absorbed when ingested, methylated, conjugated, and excreted in the urine. Acute animal toxicity studies indicate that Propyl Gallate is slightly toxic when ingested 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

Propyl Gallate is the *n*-propyl ester of gallic acid. It conforms to the following structure[1]:



Other names for this ingredient include[2]:

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.[3]

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.[2,4,5] 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.[6] 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

Property	*Value*	*Reference*
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_M	−0.52	9
Ash	0.1 percent max	5
Loss on drying	0.5 percent max	5
Inorganic Impurities† (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.
†No information is available on organic impurities.

TABLE 2. Analytical Methods Used in Propyl Gallate Determination

Method	*Reference*
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	30,31
Iron (II) ion	
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[11]:

$$LH \text{ (lipid)} + R^{\bullet} \text{ (free radical)} \rightarrow L^{\bullet} \text{ (lipid free radical)} + RH$$
$$L^{\bullet} + O_2 \rightarrow LOO^{\bullet} \text{ (lipid peroxy radical)}$$
$$LOO^{\bullet} + LH \rightarrow LOOH \text{ (oxidized lipid)} + L^{\bullet}$$

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[11]:

$$PGH \text{ (Propyl Gallate)} + LOO^{\bullet} \rightarrow LOOH + PG^{\bullet}$$
$$PG^{\bullet} + PGH \rightarrow PG\text{-}PG$$

The antioxidant activity of Propyl Gallate resides in the presence of its hydrogen-donating hydroxyl groups.[10] The oxidation of Propyl Gallate during free-radical scavenging occurs as is shown in Figure 1.[12]

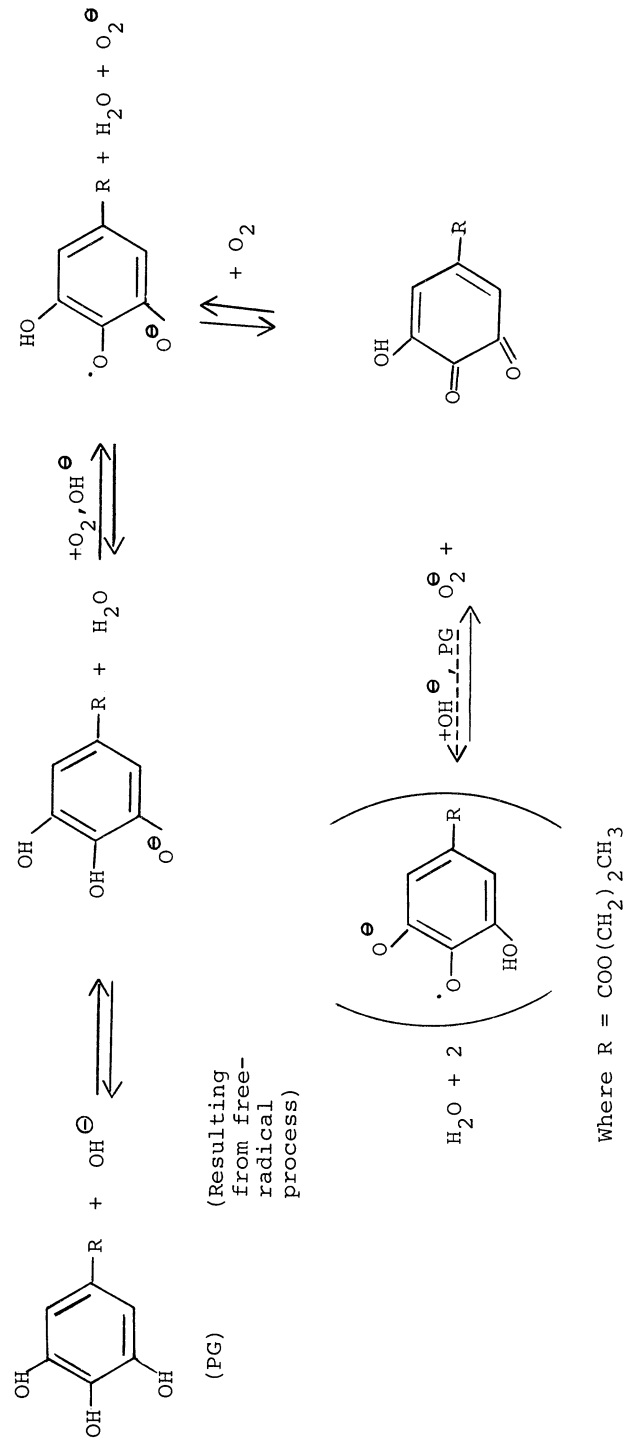


FIG. 1. Reactivity of Propyl Gallate.

Distributed for Comment Only -- Do Not Cite or Quote

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.[34] 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.[35] It discolors in the presence of iron or when it is exposed to air or light for long periods of time.[36]

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.[37]

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.[38] These mixtures usually contain up to 6 percent Propyl Gallate and are used at low concentrations in almost all product type categories.[2,38,39]

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[38]

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
Propyl Gallate						
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

Distributed for Comment Only -- Do Not Cite or Quote

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.[35,36,40]

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.[40]

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[40] 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).[40]

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.[41]

BIOLOGICAL EFFECTS

Antimicrobial Activity

Jordan et al.[42] 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.[43] Shih and Harris[44] 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

Distributed for Comment Only -- Do Not Cite or Quote

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.[45,46]

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.[47]

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.[48]

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.[49]

Gonikberg et al.[50] reported that Propyl Gallate forms a biochemical complex with flavinmononucleotide (FMN).

Inhibition of Formation of Carcinogenic Nitrosamines

Kawanishi et al.[51] 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 μmol Propyl Gallate per kg body weight; Propyl Gallate was considered a relatively strong inhibitor. Similarly, Rao et al.[52] 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.[53] Vartanyan et al.[54] observed the inactivation of lactic dehydrogenase by Propyl Gallate was due to the oxidation of sulfhydryl (SH) groups of the enzyme by Propyl Gallate

Distributed for Comment Only -- Do Not Cite or Quote

radicals (7.1×10^{-4} M). Brzhevskaya et al.[55] reported that Propyl Gallate, at concentrations of 1×10^{-3} M to 6.7×10^{-3} M, inhibited the enzymatic hydrolysis of adenosine triphosphate (ATP) 40 to 85 percent by blocking the formation of free radicals. Agatova and Emanuel[56] stated that radicals of Propyl Gallate (at concentration of 1×10^{-3} M) accelerated the conversion of SH groups of enzymes to S–S bonds under oxidation. Both the formation of S–S bonds and the destruction of SH bonds deactivate enzymes. They observed that D-glyceraldehyde-3-phosphate dehydrogenase, which contains SH groups, was affected, whereas 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.[57]

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.[58] Yang and Strickhart[59] 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 μM Propyl Gallate, respectively. Propyl Gallate did not, however, inhibit NADPH-dependent reduction of cytochrome P-450, indicating that the site of inhibition was not on NADPH-cytochrome c reductase, as Torrielli and Slater[58] had suggested. The authors believed the site of inhibition was cytochrome P-450 itself. In 1977, Rahimtula et al.[60] confirmed that Propyl Gallate (25 to 125 μM) 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[58] and Yang and Strickhart[59] may mean that the concentrations of Propyl Gallate attained in vivo were much lower than those used in vitro.[61]

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

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.[66]

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.[67] were first to demonstrate that high concentrations of Propyl Gallate inhibited prostaglandin synthesis in sheep seminal vesicles. McDonald-Gibson et al.[68] confirmed these findings (50 percent inhibitory concentration of 103 μM) using bull seminal vesicles in vitro. Panganamala et al.[69] reported that Propyl Gallate, at concentrations of 4×10^{-4} M, inhibited the formation of prostaglandin from eicosa-8,11,14-trienoic acid by bovine seminal vesicle microsomes.

Beetens and Herman[70] observed that Propyl Gallate enhanced the formation of 6-oxo-$PGF_{1\alpha}$ 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.[69]

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 $PGF_{2\alpha}$ but had no effect on PGE_2. It was suggested that Propyl Gallate scavenged the oxygen radical formed during the conversion of PGG_2 to PGH_2 and, consequently, altered the amount and types of prostaglandins produced by the mammary gland.[71]

Propyl Gallate altered prostaglandin endoperoxide synthetase and peroxidase activities of seminal vesicle microsomes. At 0.1 mM Propyl Gallate, production of $PGF_{2\alpha}$ and PGE_2 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 $PGF_{2\alpha}$ and PGI_2 than did controls. Exogenous Propyl Gallate stimulated production of $PGF_{2\alpha}$ and PGE_2 in rats fed control diets and rats fed vitamin E-deficient diets. The author concluded that Propyl Gallate had a concentration-dependent effect on the biosynthesis of prostaglandins by regulating the availability of lipid peroxide intermediate.[72]

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-

Distributed for Comment Only -- Do Not Cite or Quote

tions of 10^{-6} M or greater.[73] Propyl Gallate also inhibited in vitro antibody production by mouse splenic cells at 5 μg/ml and suppressed multiplication of human and mouse cells at 20 μg/ml.[74]

The effect of Propyl Gallate on mouse lung metabolism was studied by Omaye et al.[75] 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.[76]

Modak and Rao[77] 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 μg/ml incubate). Oral and subcutaneous administration of 10 or 40 mg/kg Propyl Gallate had no effect on AA-induced contractions. The antinociceptive effect of Propyl Gallate may be due in part to its anesthetic effect and in part to deactivation of arachidonic acid.[68]

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.[78-81]

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

The effect of Propyl Gallate as an ultraviolet light protector was studied in vivo by McDonald-Gibson and Schneider.[87] 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.[88]

Chemoprotection

Propyl Gallate, in doses ranging from 30 to 300 mg/kg body weight, inhibited the toxic effects of certain chemicals in rats. These chemicals, through the formation of free-radicals, can result in lipoperoxidation (CCl_4), hepatotoxicity (acetaminophen), fatty liver (white phosphorus, CCl_4), hepatic polysomal disaggregation (white phosphorus), hemolysis of RBCs (vitamin D_2), and decreased hepatic microsome amino acid incorporation (CCl_4). Propyl Gallate acted as a free-radical scavenger and inhibited lipoperoxidation. It also inhibited cytochrome P-450 of the microsomal mixed function oxidase drug-metabolizing system; this resulted in decreased formation of potentially toxic metabolites.[89-97]

Distributed for Comment Only -- Do Not Cite or Quote

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.[98] In two studies, Propyl Gallate (25 to 125 μM and 410 nmol/plate) inhibited the mutagenic activity of benzo[a]pyrene (BP) metabolites in *S. typhimurium* strain TA98.[60,99] Rahimtula et al.[60] claimed that Propyl Gallate inhibited BP-hydroxylase in the microsomal preparation. Springarn and Garvie[100] 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.[101] 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.[102] In addition, Propyl Gallate reduced the mutagenic activity of aflatoxin B_1 in *S. typhimurium* TA98 under metabolic activation,[103] 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.[104]

Anticarcinogenesis/Antitumorigenesis

Kozumbo et al.[105] investigated the role of reactive oxygen species in tumor promotion by examining the effects of antioxidants on the 12-0-tetradecanoyl phorbol-13-acetate (TPA)-induced ornithine decarboxylase (ODC) activity. Propyl Gallate (50 μmol) applied topically to mouse epidermis substantially inhibited TPA-induced ODC activity. Propyl Gallate may inhibit the promotion phase of carcinogenesis.

McCay et al.[106] 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.[107] 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.[108] 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.[109,110] reported that Propyl Gallate inhibited protein and nucleic acid biosynthesis in Erhlich ascites carcinomas and solid hepatomas, whereas in vivo it did not affect these biosynthetic processes in healthy tissue. Furthermore, Propyl Gallate inhibited these processes in cultured human laryngeal cancer cells. Emanuel et al.[111] 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.[112] 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,[113] in experiments with isolated DNA, reported that the radioprotective effect of Propyl Gallate increased as the concentration of unoxidized Propyl Gallate (maximum effect at 1.65×10^{-2} M) increased before radiation and likewise the radioprotective effect decreased as the time of 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.[114]

Desesso[115] 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-

Distributed for Comment Only -- Do Not Cite or Quote

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. Desesso 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.[42] 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[116] 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.[117] 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.[118] 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[119] 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[120] and Booth et al.[121] 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-β: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 Proyl Gallate in rats and rabbits.

ANIMAL TOXICOLOGY

Acute Effects

Oral Toxicity

The acute oral LD_{50} of Propyl Gallate has been determined in mice (1.70 to 3.50 g/kg), rats (2.1 to 7 g/kg), hamsters (2.48 g/kg), and rabbits (2.75 g/kg). Groups of animals received the test material at one or more doses, orally or by gastric intubation. Animals were observed for up to 10 days. In a number of studies, the tissues from animals that died were examined microscopically. Results of these tests 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.[122,123] 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.[124]

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.[125,126]

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_{50} 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.[118]

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).

Distributed for Comment Only -- Do Not Cite or Quote

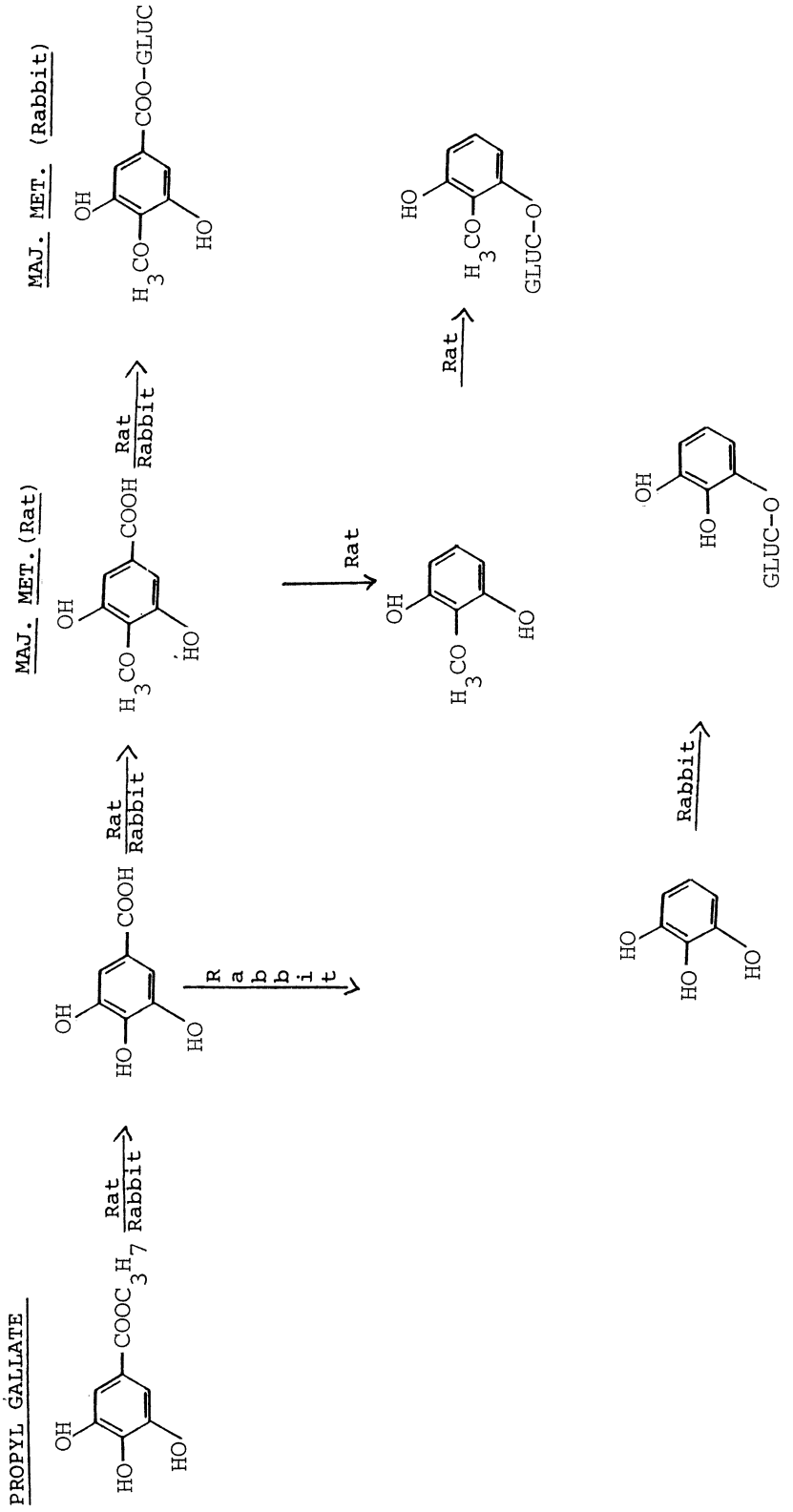


FIG. 2. Metabolic pathway of Propyl Gallate in rats and rabbits.

Distributed for Comment Only -- Do Not Cite or Quote

TABLE 4. Acute Oral Toxicity of Propyl Gallate

Animal	Number/ Group	Dose (g/kg)	LD_{50} (g/kg)	Comment/Conclusion*	Reference
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[10] (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[77] (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[132] (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

Distributed for Comment Only -- Do Not Cite or Quote

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[133] (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[134] (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[135] (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.[136] 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[137,138] (Table 6).

TABLE 6. Acute Eye Irritation of Products Containing Propyl Gallate

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

Distributed for Comment Only -- Do Not Cite or Quote

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[139,140] (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.[141]

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.[142]

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.[119]

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.[128]

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.[143]

Distributed for Comment Only -- Do Not Cite or Quote

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.[144]

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.[145]

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.[146]

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.[146]

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.

Distributed for Comment Only -- Do Not Cite or Quote

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.[146]

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.[146]

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.[118]

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.[118]

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.[118]

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.[147]

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.[39]

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.[148]

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.[119]

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.[149]

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.[118] corresponded to an intake of 0.05 g/kg per day.[150]

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

Distributed for Comment Only -- Do Not Cite or Quote

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.[151]

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.[131]

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.[131]

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.[131]

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.[152]

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.[153]

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.[154]

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.[103]

Shelef and Chin[104] 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.[155]

Mutagenesis Enhancement

Rosin and Stich[103] reported that Propyl Gallate enhanced the mutagenic effect of N-hydroxy-2-acetylaminofluorine and 4-nitroquinoline-1-oxide (4-NQO) in *S. typhimurium* strains TA98 and TA100, respectively. Bacterial cultures were suspended in a mixture of Propyl Gallate, chemical to be tested, dimethyl sulfoxide, and saline. A 580 to 700 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.

Distributed for Comment Only -- Do Not Cite or Quote

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.[156]

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.[157]

Teratogenesis

The teratogenic effect of Propyl Gallate was studied in 9 female rats by Telford et al.[158] 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.[159]

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. Ingestation 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.[160]

Desesso[115] 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 cannabilism of the newborn by the dams. No behavioral or morphological changes were observed in the newborns from test mothers. Propyl Gallate was nonteratogenic.[130]

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

Distributed for Comment Only -- Do Not Cite or Quote

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[10] (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[146] (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"[162] (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[161] (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.[163-165] 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-

Distributed for Comment Only -- Do Not Cite or Quote

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.

Distributed for Comment Only -- Do Not Cite or Quote

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[166-172] (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 erythemal dose (MED). Erythema was evaluated 24 hours later. Propyl Gallate was then reapplied 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[173] (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[174] (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

Distributed for Comment Only -- Do Not Cite or Quote

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

Distributed for Comment Only -- Do Not Cite or Quote

total UVA dosage of 4,400 $\mu W/cm^2$; 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 erythemal reactions (scores of ±, 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[166-172] (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 $\mu W/cm^2$. 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.[166-172]

The phototoxicity of a sun protection stick containing 0.003 percent Propyl Gallate was evaluated using 10 subjects. Applications of 5 ml/cm^2 of the sun stick were rubbed into the lower back of each subject and then occluded for 24 hours. Patches were removed, and the sites were radiated for 20 minutes with filtered long-wave UV light (UVA 30 mW/cm^2) using a 150W xenon solar simulator (emission of 124 mW/cm^2). 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[175] (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[176] (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.[10]

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.[177]

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

Distributed for Comment Only -- Do Not Cite or Quote

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-acetylaminofluorine 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 and RIPTs 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 percent.

ACKNOWLEDGMENT

Elizabeth Meerman Santos, Scientific Analyst and writer, prepared the technical analysis used by the Expert Panel in developing this report.

REFERENCES

1. ESTRIN, N.F. (ed.). (1975). *CTFA Cosmetic Ingredient Dictionary*, 2nd ed. Washington, DC: Cosmetic, Toiletry and Fragrance Assoc.
2. WINDHOLZ, M. (ed.). (1976). *The Merck Index*, 9th ed. Rahway, NJ: Merck & Co.
3. FOOD AND DRUG RESEARCH LABS (FDRL). (1972). GRAS (Generally Recognized As Safe) food ingredients: Propyl gallate. (PB-221 207):1-51.
4. JAPAN COSMETIC INDUSTRY ASSOCIATION (JCIA). (1979). Japanese Standards of Cosmetic Ingredients. Yakuji Nippo.
5. COSMETIC, TOILETRY AND FRAGRANCE ASSOCIATION (CTFA). (1972). Cosmetic Ingredient Specifications. Washington, DC.
6. WAN, L.S.C. (1972). Solubilization of gallates in solutions of nonionic surfactants. Can. J. Pharm. Sci. **7**(1), 25-7.
7. WEAST, R.C. (ed.). (1978). *Handbook of Chemistry and Physics*, 59th ed. Palm Beach, FL: CRC Press.
8. KAHN, G., CURRY, M.C., and DUSTIN, R. (1973). New approaches to investigating UVL (ultraviolet light) photoprotective substances in vitro. Arch. Dermatol. Forsch. **246**(3), 301-18.
9. BOYD, I., and BEVERIDGE, E.G. (1979). Relationship between the antibacterial activity towards *Escherichia coli* NCTC 5933 and the physico-chemical properties of some esters of 3,4,5-trihydroxybenzoic acid (gallic acid). Microbioscopy **24**(97-98), 173-84.
10. BOEHM, E., and WILLIAMS, R. (1943). A study of the inhibiting actions of propyl gallate (normal propyl trihydroxy benzoate) and certain other trihydric phenols on the autoxidation of animal and vegetable oils. Quart. J. Pharm. Pharmacol. **16,** 232-43.
11. GUTTERIDGE, J.M., and FU, K.C. (1981). Enhancement of bleomycin-iron free radical damage to DNA by antioxidants and their inhibition of lipid peroxidation. FEBS Lett. **123**(1), 71-4.
12. FORGO, I., and BUCHI, J. (1970). Synthesis, physical-chemical properties and antioxidative effect of some gallic acid esters. I. Nature, mechanism of action and properties of antioxidants. Pharm. Acta Helv. **45,** 207-26.
13. DAVIDEK, J. (1963). J. Chromatogr. **11,** 419.
14. MITCHELL, L.C. (1957). Separation and identification of four antioxidants, butylated hydroxyanisole, butylated hydroxytoluene, *n*-propyl gallate, and nordihydroguaiarotic acid by paper chromatography. J. Assoc. Off. Anal. Chem. **40**(3), 909-15.
15. SALO, T., and SALMINEN, K. (1964). Suomen Kemi **37**(Pt. A), 161.
16. MATTHEW, T.V., and MITRA, S.N. (1965). Separation and identification of antioxidants in oils and fats by thin-layer chromatography. Indian J. Technol. **3**(3), 102.
17. DESSEL, L. VAN, and CLEMENT, J. (1969). Thin-layer chromatographic separation of antioxidants (in fats and oils). Z. Lebensm. Unters. Forsch. **139**(3), 146-9.
18. WACHS, W., and GASSMANN, L. (1970). Determination of gallic acid esters by gas chromatography. Deutsch. Lebensm. Rundsch. **66**(2), 37-8.
19. McCAULLEY, D.F., FAZIO, T., HOWARD, J.W., DiCIURCIO, F.M., and IVES, J. (1967). The multidetermination of antioxidants in lard. J. Assoc. Off. Anal. Chem. **50**(2), 243-50.
20. BERGER, K.G., et al. (1960). Die Bestimmung Chemischer antioxydantien in Fetten nach Abtrennung durch Verteilungschromatographie. Analyst **85,** 341-6.
21. CHIANG, H., and TSENG, R. (1969). Polyamide-kieselguhr thin layer chromatography of antioxidants. J. Pharm. Sci. **58**(Dec), 1552-3.

Distributed for Comment Only -- Do Not Cite or Quote

22. DAVIDEK, J., and POKORNY, J. (1961). Detection of antioxidants in fats with the aid of thin-layer chromatography on polyamide powder. Z. Lebensm. Untersuch. Forsch. **115,** 113–7.
23. KING, W.P., JOSEPH, K.T., and KISSINGER, P.T. (1980). Liquid chromatography with amperometric detection for determining phenolic preservatives. J. Assoc. Off. Anal. Chem. **63**(1), 137–42.
24. PAGE, B.D., and KENNEDY, B.P.C. (1976). Rapid determination of butylated hydroxyanisole, tert-butylhydroquinone, and propyl gallate in edible oils by electron capture gas-liquid chromatography. J. Assoc. Off. Anal. Chem. **59**(6), 1208–12.
25. KLINE, D.A., JOE, F.L., JR., and FAZIO, T. (1978). A rapid gas-liquid chromatographic method for the multideterminination of antioxidants in fats, oils, and dried food products. J. Assoc. Off. Anal. Chem. **61**(3), 513–9.
26. PAGE, B.D. (1979). High performance liquid chromatographic determination of nine phenolic antioxidants in oils, lards, and shortenings. J. Assoc. Off. Anal. Chem. **62**(6), 1239–46.
27. LATZ, H.W., and HURTUBISE, R.J. (1969). Luminescence analysis of food antioxidants; determination of propyl gallate in lard. J. Agr. Food Chem. **17**(2), 352–5.
28. FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES. (1965). Specifications for identity and purity and toxicological evaluation of some antimicrobials and antioxidants. WHO/Food Add./24.65; FAO Nutr. Meet. Rep. Ser. No. 38A.
29. CASSIDY, W., and FISHER, A.J. (1960). Analyst **85,** 295.
30. VOS, H.J., WESSELS, H., and SIX, C.W.T. (1957). Analyst **82,** 362.
31. CHATT, E.M. (June 1962). A survey of methods for the detection and determination of antioxidants in fats and foods. British Food Manufacturing Industries Res. Assoc. Tech Circa No. 206:45 (BEMIRA: Leatherhead, Surrey, England).
32. ASSOCIATION OF PUBLIC ANALYSTS (APA). (1963). The detection and determination of antioxidants in food. Spec. Rep. **1,** 8.
33. PARODI, P.W. (1965). Austral. J. Dairy Technol. **20,** 6.
34. SEN, N.P., DONALDSON, B., SEAMAN, S., IYENGAR, J.R., and MILES, W.F. (1976). Inhibition of nitrosamine formation in fried bacon by propyl gallate and L-ascorbyl palmitate. J. Agr. Food Chem. **24**(2), 397–401.
35. BENTZ, R.W., O'GRADY, T.J., and WRIGHT, S.B. (1952). Antioxidants and food preservation. Food Technol. **6**(8), 302–4.
36. PERFUME AND FLAVOR CHEMICALS. (1969). Steffan Arctander, Pub.
37. BALSAM, M.S., and SAGARIN, E. (eds.). (1974). *Cosmetics: Science and Technology*, 2nd ed. New York: John Wiley & Sons.
38. FOOD AND DRUG ADMINISTRATION (FDA). (December 1981). Cosmetic product formulation data. Computer printout. Washington, DC.
39. GRAHAM, W.D., TEED, H., and GRICE, H.C. (1954). Chronic toxicity of bread additives to rats. J. Pharm. Pharmacol. **6,** 534–45.
40. LIFE SCIENCES RESEARCH OFFICE (LSRO). (1973). Evaluation of the health aspects of propyl gallate as a food ingredient. (PB-223 840), 1–13.
41. JOHNSON, F.C. (October 1971). A critical review of the safety of phenolic antioxidants in foods. CRC Crit. Rev. Food Tech. pp. 267–304.
42. JORDAN, H.V., BOWLER, A.E., and BERGER, N.D. (1961). Testing of antioxidants against experimental caries in rats. J. Dental Res. **40**(5), 878–883.
43. BAJAJ, I., VERMA, K.K., PRAKASH, O.M., and PARIHAR, D.B. (1970). Separation of alkyl gallates as complexes with cinchonine and strychnine. J. Chromatogr. **46**(3), 261–6.
44. SHIH, A.L., and HARRIS, N.D. (1977). Antimicrobial activity of selected antioxidants. J. Food Prot. **40**(8), 520–2.
45. ANDREWS, F.A., BEGGS, W.H., and SAROSI, G.A. (1977). Influence of antioxidants on the bioactivity of amphotericin B. Antimicrob. Agents Chemother. **11,** 615–8.
46. BEGGS, W.H., ANDREWS, F.A., and SAROSI, G.A. (1978). Antioxidant enhancement of amphotericin B activity against *Candida albicans.* Res. Commun. Chem. Pathol. Pharmacol. **20**(2), 409–12.
47. KOK, I.P. (1960). The effect of propyl gallate on the nucleic acid concentration in healthy and virus-infected cocoons of the oak silkworm. Dokl. Biochem. **130,** 27–8 (trans. from Dokl. Akad. Nauk SSSR **130,** 1141–4).
48. RIZZUTO, F., and SPIKES, J.D. (1975). Mechanisms involved in the chemical inhibition of the eosin-sensitized photooxidation of trypsin. Radiat. Environ. Biophys. **12**(3), 217–32.
49. SCHUH, J., FAIRCLOUGH, G.F., JR., and HASCHEMEYER, R.H. (1978). Oxygen-mediated heterogeneity of apo-low-density lipoprotein. Proc. Natl. Acad. Sci. USA **75**(7), 3173–7.
50. GONIKBERG, E.M., VARTANYAN, L.S., MAMAYEVA, O.K., and EMANUEL, N.M. (1967). Complex formation in the flavin mononucleotide-H–propylgallate system. Biofizika **12,** 814–9.

51. KAWANISHI, T., OHNO, Y., TAKAHASHI, A., ISHIWATA, H., TANIMURA, A., KASUYA, Y., and OMORI, Y. (1981). Studies on nitrosamine formation by the interaction between drugs and nitrite. I. Measurement of the amount of nitrosamine formed in rat and guinea pig stomachs. J. Toxicol. Sci. **6**(4), 261–86.
52. RAO, G.S., OSBORN, J.C., and ADATIA, M.R. (1982). Drug-nitrite interactions in human saliva: effects of food constituents on carcinogenic *n*-nitrosamine formation. J. Dent. Res. **61**(6), 768–71.
53. NEIFAKH, E.A. (1962). Specific inhibition of activity of reduction-oxidation enzymes of glycolysis of inhibitors of free-radical reactions. Dokl. Akad. Nauk SSSR **142,** 1405–8.
54. VARTANYAN, L.S., GONIKBERG, E.M., and EMANUEL, N.M. (1964). Kinetics of lactic dehydrogenase inactivation with free-radical products of propyl gallate autoxidation. Izv. Akad. Nauk SSSR Ser. Khim. **10,** 1742–8.
55. BRZHEVSKAYA, O.N., KAYUSHIN, L.P., and NEDELINA, O.S. (1966). Existence of free radicals during enzymic hydrolysis of ATP. Biofizika **11**(2), 213–6.
56. AGATOVA, A.I., and EMANUEL, N.M. (1966). The effect of propyl gallate on SH- and SS-containing enzymes. Biokhimiya (Moscow) **31**(2), 299–305.
57. LEVITT, M., GOBB, J.W., DALY, J.W., LIPTON, M., and UNDENFRIEND, S. (1967). A new class of tyrosine hydroxylase inhibitors and a simple assay of inhibition in vivo. Biochem Pharmacol. **16**(7), 1313–21.
58. TORRIELLI, M.V., and SLATER, T.E. (1971). Inhibition of NADPH-cytochrome C reductase by propyl gallate. Biochem. Pharmacol. **20,** 2027–32.
59. YANG, C.S., and STRICKHART, F.S. (1974). Inhibition of hepatic mixed function oxidase activity by propyl gallate. Biochem. Pharmacol. **23**(22), 3129–38.
60. RAHIMTULA, A.D., ZACHARIAH, P.K., and O'BRIEN, P.J. (1977). The effects of antioxidants on the metabolism and mutagenicity of benzo(a)pyrene in vitro. Biochem. J. **164**(1), 473–5.
61. KING, M.M., and McCAY, P.B. (1981). Studies on liver microsomes of female rats fed purified diets varying in fat content and with and without propyl gallate. Food Cosmet. Toxicol. **19**(1), 13–18.
62. AUTRUP, H., and WARWICK, G.P. (1975). Characteristics of two azoreductase systems in rat liver. Chem. Biol. Interact. **11**(5), 329–42.
63. SIETSEMA, W.K., and DeLUCA, H.F. (1979). In vitro epoxidation of all-trans-retinoic acid in rat tissue homogenates. Biochem. Biophys. Res. Commun. **90**(4), 1091–7.
64. ICHIHARA, K., EL-ZAYAT, M., MITTAL, C.K., and MURAD, F. (1979). Fatty acid activation of guanylate cyclase from fibroblasts and liver. Arch. Biochem. Biophys. USA **197**(1), 44–51.
65. PARADISI, L., NEGRO, F., PANAGINI, O., and TORRIELLI, M.V. (1979). Interference of antioxidants E/O of some free radical scavengers: with the activity of glucose-6-phosphatase after administration of carbon tetrachloride. Boll. Soc. Ital. Biol. Sper. **55**(18), 1977–83.
66. LAKE, B.G., LONGLAND, R.C., HARRIS, R.A., COLLINS, M.A., HEROD, I.A., and GANGOLLI, S.D. (1980). The effect of treatment with some phase II substrates on hepatic xenobiotic metabolism and the urinary excretion of metabolites of the D-glucuronic acid pathway in the rat. Toxicol. Appl. Pharmacol. **52**(3), 371–8.
67. NUGTEREN, D.H., et al. (1966). The enzymic conversion of all-cis-8,11,14-eicosatrienoic acid into prostaglandin E. Rec. Trav. Chem. **85**(4), 405–19.
68. McDONALD-GIBSON, W.J., SAEED, S.A., and SCHNEIDER, C. (1976). The local antinociceptive and topical anti-inflammatory effects of propyl gallate in rodents. Br. J. Pharmacol. **58**(4), 573–81.
69. PANGANAMALA, R.V., MILLER, J.S., GWEBU, E.T., SHARMA, H.M., and ORNWELL, D.G. (1977). Differential inhibitory effects of vitamin E and other antioxidants on prostaglandin synthetase, platelet aggregation and lipoxidase. Prostaglandins **14**(2), 261–71.
70. BEETENS, J.R., and HERMAN, A.G. (1980). Enhanced formation of 6-oxo-PGF1 alpha by ram seminal vesicle microsomes in the presence of antioxidants. Br. J. Pharmacol. **69**(2), 267P–8P.
71. TO, D., SMITH, F.L., and CARPENTER, M.P. (1980). Mammary gland prostaglandin synthesis: Effect of dietary lipid and propyl gallate. Adv. Prostaglandin Thromboxane Res. **8,** 1807–12.
72. CARPENTER, M.P. (1981). Antioxidant effects on the prostaglandin endoperoxide synthetase product profile. Fed. Proc. **40**(2), 189–94.
73. BETTGER, W.J., and HAM, R.G. (1981). Effects of nonsteroidal anti-inflammatory agents and antioxidants on the clonal growth of human diploid fibroblasts. Prog. Lipid Res. **20**(1–4), 265–8.
74. BLALOCK, J.E., ARCHER, D.L., and JOHNSON, H.M. (1981). Anticellular and immunosuppressive activities of food-borne phenolic compounds. Proc. Soc. Exp. Biol. Med. **167**(3), 391–3.
75. OMAYE, S.T., REDDY, K.A., and CROSS, C.E. (1977). Effect of butylated hydroxytoluene and other antioxidants on mouse lung metabolism. J. Toxicol. Environ. Health **3**(5–6), 829–36.
76. POSATI, L.P., FOX, K.K., and PALLANSCH, M.J. (1970). Inhibition of bradykinin by gallates. J. Agric. Food Chem. **18**(4), 632–5.

77. MODAK, A.T., and RAO, M.R. RA. (1971). Propyl gallate as a local anesthetic agent. Indian J. Med. Res. **59**(5), 795–8.
78. ERSHOFF, B.H., and STEERS, C.W., JR. (1960). Antioxidants and survival time of mice exposed to multiple sublethal doses of x-irradiation. Proc. Soc. Exp. Biol. Med. **104,** 274–6.
79. GORODETSKII, A.A., BARBABOI, V.A., and CHERNETSKII, V.P. (1961). Protective action of some inhibitors of the chain oxidative processes during the acute radiation syndrome. Radiobiologiya **1,** 781–8.
80. LIPKAN, M.F., BARABOI, V.A., and LUKASHOVA, R.G. (1962). Nucleic acids in rat organs and the effects of roentgen radiation and propyl gallate. Ukr. Biokhim. Zh. **34,** 167–75.
81. ISUPOVA, L.S., and BALABUKHA, V.S. (1963). Prevention of radiation-induced depolymerization of deoxyribonucleic acid (DNA) of rat liver by means of propyl gallate and 5-methoxy-tryptamine. Radiobiologiya **3**(2), 256–8.
82. EMANUEL, N.M., et al. (1960). Inhibition of biosynthesis of cell proteins of Yoshida ascitic hepatoma by action of inhibitors of free radical processes. Doklady Akad. Nauk SSSR **134,** 1475–7.
83. PARKHOMENKO, I.M. (1963). Effect of some radioprotectors under γ-irradiation of the cells of cynomolgus monkey heart in vitro. Radiobiologiya **3**(3), 467–71.
84. SHENG, P., WANG, H., and SHEN, Z. (1982). Transfer of radiation-induced spins from deoxyribonucleic and thymidylic acids to Propyl Gallate. Sci. Sin. (Engl. Ed.) **25**(5), 473–84.
85. WILLIAMS, D.S., and SLATER, T.F. (1973). Photosensitization of isolated lysosomes. Biochem. Soc. Trans. **1**(1), 200–2.
86. BEN-HUR, E., GREEN, M., PRAGER, A., ROSENTHAL, I., and RIKLIS, E. (1981). Differential protective effects of antioxidants against cell killing and mutagenesis of *Salmonella typhimurium* by gamma radiation. J. Radiat. Res. (Tokyo) **22**(2), 250–57.
87. McDONALD-GIBSON, W.J., and SCHNEIDER, C. (1974). A novel method for evaluating antiinflammatory drugs in the conscious guinea pig. Br. J. Pharmacol. **52**(1), 1–149.
88. LAW, E., and LEWIS, A.J. (1977). The effect of systemically and topically applied drugs on ultraviolet-induced erythema in the rat. Br. J. Pharmacol. **59**(4), 591–7.
89. DIANZANI, M.U., and UGAZIO, G. (1973). Lipoperoxidation after carbon tetrachloride poisoning in rats previously treated with antioxidants. Chem. Biol. Interact. **6**(2), 67–79.
90. GRAVELA, E., GABRIEL, L., and UGAZIO, G. (1971). Protection by glutathione and propyl gallate on the impaired in vitro amino acid incorporation into liver microsomal protein of carbon tetrachloride-poisoned rats. Biochem. Pharmacol. **20**(8), 2065–70.
91. SLATER, T.F., and SAWYER, B.C. (1971). Stimulatory effects of carbon tetrachloride on peroxidative reactions in rat liver fractions in vitro. Inhibitory effects of free-radical scavengers and other agents. Biochem. J. **123**(5), 823–8.
92. TORRIELLI, M.V., and UGAZIO, G. (1975). Biochemical aspects of the protective action of propyl gallate on liver injury in rats poisoned with carbon tetrachloride. Toxicol. Appl. Pharmacol. **34**(1), 151–69.
93. SPIRICHEV, V.B., and BLAZHEVICH, N.V. (1968). The hemolytic action of vitamin D_2. Formation of lipoperoxides. Vopr. Med. Khim. **14**(4), 371–5.
94. DIANZANI, M.U. (1972). Liver steatosis induced by white phosphorus. Morgagni **5**(1), 1–23.
95. PANI, P., GRAVELA, E., MAZZARINO, C., and BURDINO, E. (1972). Mechanism of fatty liver in white phosphorus poisoned rats. Exp. Mol. Pathol. **16**(2), 201–9.
96. ASTILL, B.D., and MULLIGAN, T. (1977). Phenolic antioxidants and the inhibition of dimethylamine-nitrite-induced hepatotoxicity in the rat. (Meeting Abstract). Toxicol. Appl. Pharmacol. **41**(1), 163–4.
97. KELLEHER, J., WALKER, B.E., KEANEY, N.P., LOSOWSKY, M.S., and DIXON, M.F. (1976). Modification of paracetamol toxicity by antioxidants. Biochem. Soc. Trans. **4**(2), 292–4.
98. LO, L.W., and STICH, H.F. (1978). The use of short-term tests to measure the preventive action of reducing agents on formation and activation of carcinogenic nitroso compounds. Mutat. Res. **57**(1), 57–67.
99. CALLE, L.M., and SULLIVAN, P.D. (1982). Screening of antioxidants and other compounds for antimutagenic properties towards benzo[a]pyrene-induced mutagenicity in strain TA98 of *Salmonella typhimurium*. Mutat. Res. **101**(2), 99–114.
100. SPINGARN, N.E, and GARVIE, C.T. (1979). Formation of mutagens in sugar-ammonia model systems. J. Agr. Food Chem. **27**(6), 1319–21.
101. ROSIN, M.P., and STICH, H.F. (1979). Assessment of the use of the *Salmonella* mutagenesis assay to determine the influence of antioxidants on carcinogen-induced mutagenesis. Int. J. Cancer **23**(5), 722–7.
102. FUKUHARA, Y., YOSHIDA, D., and GOTO, F. (1981). Reduction of mutagenic products in the presence of polyphenols during pyrolysis of protein. Agric. Biol. Chem. **45**(5), 1061–66.
103. ROSIN, M.P., and STICH, H.F. (1980). Enhancing and inhibiting effects of propyl gallate on carcinogen-induced mutagenesis. J. Environ. Pathol. Toxicol. **4**(1), 159–68.

104. SHELEF, L.A., and CHIN, B. (1980). Effect of phenolic antioxidants on the mutagenicity of aflatoxin B_2. Appl. Environ. Microbiol. **40**(6), 1039–43.
105. KOZUMBO, W.J., SEED, J.L., and KENSLER, T.W. (1982). Antioxidants: Potent inhibitors of 12-o-tetradecanoyl phorbol-13-acetate (TPA)-induced ornithine decarboxylase (ODC) activity in mouse epidermis. Proc. Am. Assoc. Cancer Res. **23,** 395.
106. McCAY, P.B., KING, M.M., and PITHA, J.V. (1981). Evidence that the effectiveness of antioxidants as inhibitors of 7,12-dimethylbenz[a]anthracene-induced mammary tumors is a function of dietary fat composition. Cancer Res. **41**(9), 3745–7.
107. EMANUEL, N.M., LIPCHINA, L.P., and PELEVINA, I.I. (1959). Selective lowering of the RNA content of tumor cells and their loss of implantability after treatment in vitro with inhibitors of chain reactions. Dokl. Biochem. **125,** 89–92.
108. LIPCHINA, L.P., SHIYATAYA, O.K., AFANASEV, G.G., and EMANUEL, N.M. (1960). Suppression of mitosis in a culture of human cancer cells by inhibitors of free radical reactions. Dokl. Biol. Sci. **131,** 204–6 (transl. from Dokl. Akad. Nauk SSSR **131,** 667–9).
109. KUKUSHKINA, G.V., GORBACHEVA, L.B., and EMANUEL, N.M. (1966). Inhibition of protein and nucleic acid biosynthesis by phenols in vivo. Vopr. Med. Khim. **12**(5), 452–5.
110. KUKUSHKINA, G.V., GORBACHEVA, L.B., and EMANUEL, N.M. (1966). Effect of phenolic compounds on the biosynthesis of protein and nucleic acids in cells of human laryngeal cancer Hep-2. Vopr. Onkol. **12**(5), 54–6.
111. EMANUEL, N.M., DEDERER, L.Y., KUKUSHKINA, G.V., and GORBACHEVA, L.B. (1976). Supression of RNA synthesis by propyl gallate in the RNA-polymerase system. Izv. Akad. Nauk SSSR Ser. Biol. **4,** 517–9.
112. APHANASJEV, G.G., PELEVINA, I.I., LIPCHINA, L.P., and EMANUEL, N.M. (1968). Enhancement of radiation by antioxidants. Izv. Akad. Nauk SSSR Ser. Biol. (3):333–44.
113. ODINTSOVA, S.P., and KRUGLYAKOVA, K.E. (1976). Dual nature of effect of propyl gallate on DNA subjected to irradiation. Dokl. Biophys. USA **226–228,** 9–12.
114. KING, D.W. (1964). Comparative effects of certain antioxidants on gestational performance and teratogeny in vitamin E deficient rats. J. Nutr. **83,** 123–32.
115. DESESSO, J.M. (1981). Amelioration of teratogenesis: I. Modification of hydroxyurea-induced teratogenesis by the antioxidant propyl gallate. Teratology **24**(1), 19–35.
116. LISANTI, V.F., and EICHEL, B. (1963). Antioxidant inhibition of experimentally induced caries in hamsters. J. Dent. Res. **42**(4), 1030–5.
117. THOMPSON, D.T., VOGEL, J.J., and PHILLIPS, P.H. (1965). Certain organic substances and their effects on the incidence of dental caries in the cotton rat. J. Dent. Res. **44**(3), 596–9.
118. ORTEN, J.M., KUYPER, A.C., and SMITH, A.H. (1948). Studies on the toxicity of propyl gallate and of antioxidant mixtures containing propyl gallate. Food Technol. **2**(4), 308–16.
119. VAN ESCH, G.J. (1955). The toxicity of the antioxidants propyl-, octyl-, and dodecylgallate. Voeding **16,** 683–6.
120. DACRE, J.C. (1960). Metabolic pathways of the phenolic antioxidants. J. N.Z. Inst. Chem. **24,** 161–71.
121. BOOTH, A.N., MASRI, M.S., ROBBINS, D.J., EMERSON, O.H., JONES, F.T., and DEEDS, F. (1959). Die Umwandlung von Gallussaure und verwandten Verbindungen im Stoffwechsel. J. Biol. Chem. **234,** 3014–6.
122. STILLMEADOW. (November 29, 1977). Submission of data by CTFA. Unpublished acute oral toxicity study in rats of a lipstick containing Propyl Gallate (2-8-3).*
123. STILLMEADOW. (November 29, 1977). Submission of data by CTFA. Unpublished acute oral toxicity study in rats of a lipstick containing propyl gallate (2-8-4).*
124. CTFA. (August 7, 1980). Submission of data. Unpublished acute oral toxicity study of a lipstick containing propyl gallate (2-8-6).*
125. CTFA. (December 21, 1976). Submission of data. Unpublished acute oral toxicity study of a sun protection stick containing propyl gallate.*
126. CTFA. (June 15, 1977). Submission of data. Unpublished acute oral toxicity test on a suntan butter containing propyl gallate.*
127. LEHMAN, A.J. (1950). Some toxicological reasons why certain chemicals may or may not be permitted as food additives. Assoc. Food and Drug Officials US Quart. Bull. **14,** 82–98.

*Available upon request: Administrator, Cosmetic Ingredient Review, 1110 Vermont Ave., NW, Suite 810, Washington, DC 20005.

Distributed for Comment Only -- Do Not Cite or Quote

128. KARPLYUK, I.A. (1959). Toxicologic characteristics of phenolic antioxidants of edible fats. Voprosy Pitaniya **18**(4), 24–9.
129. DANIYALOV, M.A. (1966). Hygienic assessment of a mixture containing antioxidants of alimentary fats: butylhydroxyanisole and propyl gallate. Vopr. Pitan. **25**(6), 47–51.
130. TANAKA, S., KAWASHIMA, K., NAKAURA, S., NAGAO, S., and OMORI, Y. (1979). Effect of dietary administration of propyl gallate during pregnancy on prenatal and postnatal developments of rats. Shokuhin Eiseigaku Zasshi **20**(5), 378–84.
131. LITTON BIONETICS. (1974). Mutagenic evaluation of compound FDA 71-39, propyl gallate. (PB-245 441), 1–138.
132. CTFA. (August 7, 1980). Submission of data. Unpublished primary skin irritation and corrosivity study of a lipstick containing propyl gallate (2-8-8).*
133. CTFA. (April 14, 1977). Submission of data. Unpublished primary skin irritation test on a suntan butter containing propyl gallate.*
134. CTFA. (June 19, 1980). Submission of data. Unpublished primary skin irritation test on a suntan oil containing propyl gallate.*
135. CTFA. (August 7, 1980). Submission of data. Unpublished acute eye irritation study of a lipstick containing propyl gallate (2-8-5).*
136. DRAIZE, J.H. (1959). Dermal toxicity in appraisal of the safety of chemicals. In: *Foods, Drugs and Cosmetics.* Division of Pharmacology, FDA, Dept. of HEW. Assoc. of Food and Drug Officials of the US Business Office, Bureau of Food and Drugs, Austin, Texas, pp. 46–59.
137. CTFA. (January 18, 1977). Submission of data. Unpublished acute eye irritation study of a sun protection stick containing propyl gallate.*
138. CTFA. (May 11, 1977). Submission of data. Unpublished acute eye irritation test on a suntan butter containing propyl gallate.*
139. CTFA. (November 9, 1981). Submission of data. Unpublished acute eye irritation test on three cosmetic formulations containing propyl gallate.*
140. CTFA. (November 17, 1981). Submission of data. Unpublished acute eye irritation test on three cosmetic formulations containing propyl gallate.*
141. RILEY, P.A., and SEAL, P. (1974). The role of substituted anisoles in epidermal microinvasion. J. Pathol. **114**(1), 1–7.
142. GELLIN, G.A., MAIBACH, H.I., MISIASZEK, M.H., and RING, M. (1979). Detection of environmental depigmenting substances. Contact Dermatitis **5**(4), 201–13.
143. JOHNSON, A.R., and HEWGILL, F.R. (1961). The effect of the antioxidants, butylated hydroxyanisole, butylated hydroxy toluene and propyl gallate on growth, liver and serum lipids and serum sodium levels of the rat. Aust. J. Exp. Biol. Med. Sci. **39**(4), 353–60.
144. KARPLYUK, I.A. (1968). Study of the enzyme secretory function of the small intestine and pancreas mucosa in rats fed a diet containing phenol antioxidants. Vopr. Pitan. **27**(2), 21–6.
145. FEUER, G., et al. (1965). Liver response tests. VI. Application to a comparative study of food antioxidants and hepatotoxic agents. Food Cosmet. Toxicol. **3**(3), 457–69.
146. KAHN, G., PHANUPHAK, P., and CLAMAN, H.N. (April 1974). Propyl gallate contact sensitization and orally-induced tolerance. Arch. Dermatol. **109,** 506–9.
147. LEHMAN, A.J., FITZHUGH, O.G., NELSON, A.A., and WOODARD, G. (1951). Pharmacological evaluation of antioxidants. Adv. Food Res. **3,** 200.
148. GRAHAM, W.D., and GRICE, H.C. (1955). Chronic toxicity of bread additives to rats. II. J. Pharm. Pharmacol. **7,** 126–34.
149. TARJAN, R., et al. (1965). Effects produced on warm-blooded animals by admixtures and adjuvants contained in foodstuffs of Hungarian origin. Vopr. Pitan. **24**(5), 11–7.
150. DACRE, J.C. (1974). Long-term toxicity study of *n*-propyl gallate in mice. Food Cosmet. Toxicol. **12**(1), 125–9.
151. CTFA. (September 27, 1977). Submission of data. Unpublished phototoxicity test on a sun protection stick containing propyl gallate.*
152. ISHIDATE, M.J., HAYASHI, M., SAWADA, M., MATSUOKA, A., and YOSHIKAWA, K. (1978). Cytotoxicity test on medical drugs. Chromosome aberration tests with Chinese hamster cells in vitro. Eisei Shikensho Hokoku **96,** 55–61.
153. SASAKI, M., SUGIMURA, K., YOSHIDA, M.A., and ABE, S. (1980). Cytogenetic effects of 60 chemicals on cultured human and Chinese hamster cells. Senshokutai **20,** 574–84.
154. SIMMON, V.F., and ECKFORD, S.L. (1978). Microbial mutagenesis testing of substances. Compound report: F76-Q12, propyl gallate. Report (L5U-6909):14.

155. KAWACHI, T., YAHAGI, T., KADA, T., TAZIMA, Y., ISHIDATE, M., SASAKI, M., and SUGIYAMA, T. (1980). Cooperative program on short-term assays for carcinogenicity in Japan. IARC (Int. Agency Res. Cancer) Sci. Publ. **27,** 323–30.
156. STONER, G.D., SHIMKIN, M.B., KNIAZEFF, A.J., and WEISBURGER, J.H. (1973). Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A mice. Cancer Res. **33**(12), 3069–85.
157. NATIONAL TOXICOLOGY PROGRAM (NTP). (December 1982). Carcinogenesis bioassay for propyl gallate in F344 rats and B63CF$_1$ mice. NTP-81-42, NIH Publication No. 83-1796.
158. TELFORD, I.R., WOODRUFF, C.S., and LINFORD, R.H. (1962). Fetal resorption in the rat as influenced by certain antioxidants. Am. J. Anat. **110,** 29–36.
159. FDRL. (1972). Teratologic evaluation of FDA 71-39 (propyl gallate). (PB-221 790):1–42.
160. FDRL. (1973). Teratologic evaluation of FDA 71-39 (propyl gallate). (PB-223 816):1–14.
161. HILL TOP RESEARCH. (January 5, 1978). Submission of data by CTFA. Unpublished study of cumulative irritant properties of test materials, (2-8-2).*
162. CTFA. (October 2, 1980). Submission of data. Unpublished repeated insult patch test (RIPT) of a lipstick containing propyl gallate (2-8-7).*
163. CTFA. (September 12, 1980). Submission of data. Unpublished RIPT on a suntan oil containing propyl gallate.*
164. CTFA. (June 20, 1977). Submission of data. Unpublished RIPT on a suntan butter containing propyl gallate.*
165. CTFA. (March 1, 1977). Submission of data. Unpublished repeat insult patch test on a sun protection stick containing propyl gallate.*
166. FDRL. (July 31, 1981). Clinical safety evaluation (photoallergy series) of sunscreen formulation: SP-104-L-3A.
167. FDRL. (July 31, 1981). Clinical safety evaluation (photoallergy series) of sunscreen formulation: SP-104-L-3B.
168. FDRL. (December 3, 1981). Clinical safety evaluation (photoallergy series) of sunscreen formulation: SP-104-L-5.
169. FDRL. (December 31, 1981). Clinical safety evaluation (photoallergy series) of sunscreen formulation: SP-107-1.
170. FDRL. (December 31, 1981). Clinical safety evaluation (photoallergy series) of sunscreen formulation: SP-107-4.
171. FDRL. (July 2, 1981). Clinical safety evaluation (photoallergy series) of sample: SP-103-3-A, a cosmetic formulation containing propyl gallate.
172. FDRL. (July 2, 1981). Clinical safety evaluation (photoallergy series) of sample: SP-103-3-E, a cosmetic formulation containing propyl gallate.
173. KAHN, G., and CURRY, M.C. (1974). Ultraviolet light protection by several new compounds. Arch. Dermatol. **109,** 510–7.
174. CTFA. (February 28, 1977). Submission of data. Unpublished photocontact allergy test on a sun protection stick containing propyl gallate.*
175. CTFA (February 28, 1977). Submission of data. Unpublished phototoxicity test on a sun protection stick containing propyl gallate.*
176. CTFA. (September 25, 1980). Submission of data. Unpublished controlled use test on a suntan oil containing propyl gallate.*
177. NITZAN, M., VOLOVITZ, B., and TOPPER, E. (1979). Infantile methemoglobinemia caused by food additives. Clin. Toxicol. **15**(3), 273–80.

Distributed for Comment Only -- Do Not Cite or Quote

International Journal of Toxicology, 26(Suppl. 3):89–118, 2007
Copyright © American College of Toxicology
ISSN: 1091-5818 print / 1092-874X online
DOI: 10.1080/10915810701663176

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

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

INTRODUCTION

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

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

CHEMISTRY

Definition and Structure

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

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

Chemical and Physical Properties

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

Received 14 May 2007; accepted 24 August 2007.

Address correspondence to Lillian Becker, CIR Scientific Writer/Analyst, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036, USA. Former staff member Eric Hooker also contributed.

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

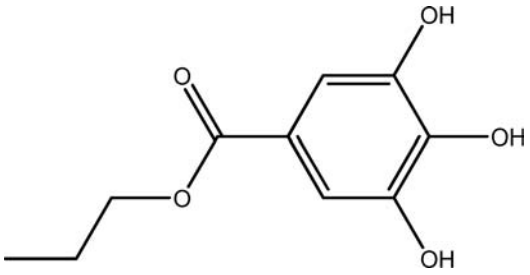


FIGURE 1
Chemical structure of Propyl Gallate (Gottshcalck and McEwen 2004).

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

TABLE 1
Physical and chemical properties of Propyl Gallate

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

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

Method of Manufacture

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

Analytical Methods

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

Reactivity

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

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

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

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

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

The oxidation of Propyl Gallate during free-radical

TABLE 2
Analytical methods used in Propyl Gallate determination

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

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

USE

Cosmetic Use

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

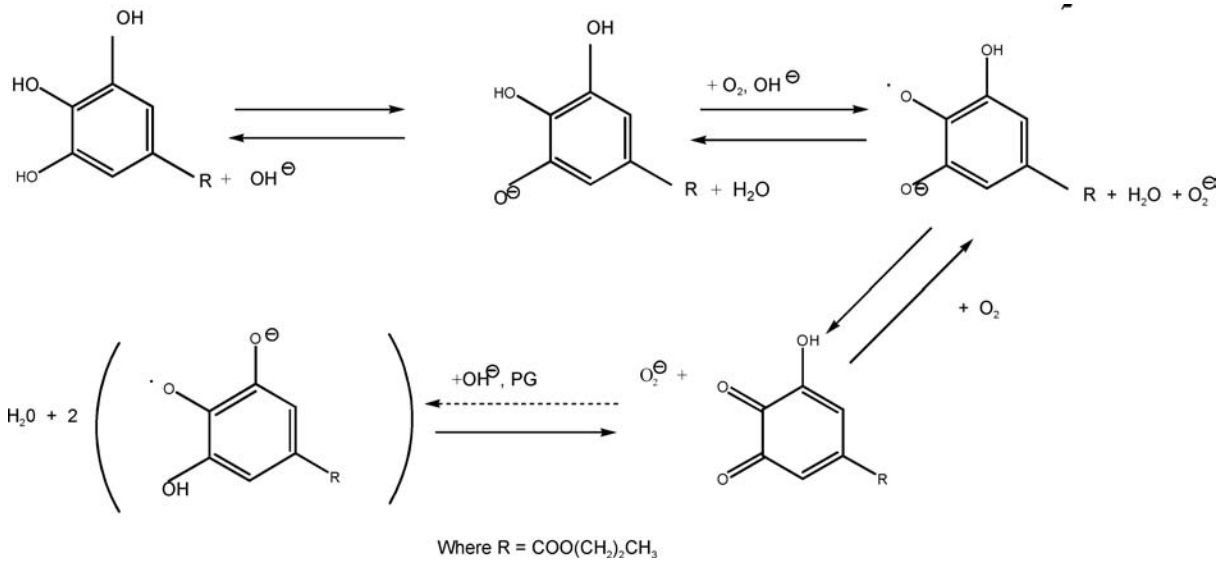


FIGURE 2
Oxidation of Propyl Gallate during free-radical scavenging suggested by Forgo and Buchi (1970).

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

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

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

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

NONCOSMETIC USE

Food

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

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

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

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

BIOLOGICAL ACTIVITY

Absorption, Metabolism, and Excretion

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

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

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

Antioxidant-Related Effects

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

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

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

(*Continued on next page*)

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

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

*No longer a category.

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

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

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

Antibacterial Activity

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

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

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

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

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

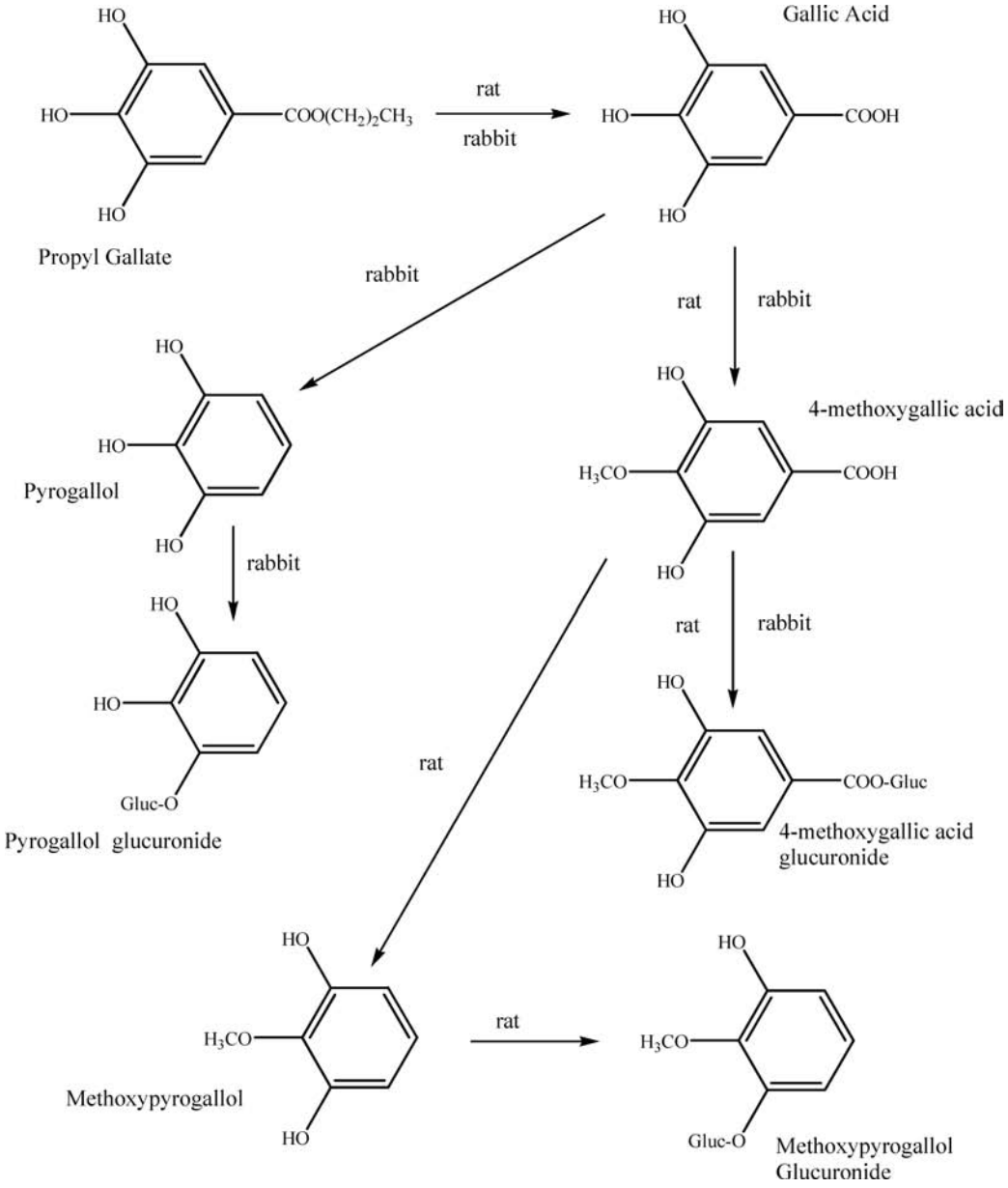


FIGURE 3
Metabolism of Propyl Gallate in rats and rabbits (after Dacre 1960).

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

Antifungal Activity

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

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

Effects on Enzymes

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

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

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

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

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

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

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

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

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

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

Effects on Prostaglandins/Anti-inflammatory Effects

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

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

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

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

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

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

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

Cellular/Tissue Effects

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

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

Hepatotoxicity/Hepatoprotection

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

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

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

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

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

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

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

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

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

Coagulant Effects

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

Neurological/Neuromuscular Effects

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

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

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

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

Anticariogenesis

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

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

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

Ionizing/Ultraviolet Radiation Protection

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

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

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

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

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

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

Chemoprotection

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

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

ANIMAL TOXICOLOGY

Acute Effects

Oral Toxicity

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

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

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

TABLE 4
Acute oral toxicity of Propyl Gallate

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

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

Intraperitoneal Toxicity

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

Dermal Irritation

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

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

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

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

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

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

TABLE 5
Acute dermal irritation of Propyl Gallate

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

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

Acute Ocular Irritation

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

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

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

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

TABLE 6
Acute ocular irritation—product tests

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

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

Subchronic Effects

Oral Toxicity

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

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

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

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

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

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

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

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

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

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

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

Dermal Toxicity

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

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

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

Chronic Oral Toxicity

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

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

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

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

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

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

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

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

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

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

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

Dermal Sensitization

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

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

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

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

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

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

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

Phototoxicity

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

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

GENOTOXICITY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Mutagenesis Enhancement

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

Antimutagenesis

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

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

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

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

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

CARCINOGENICITY

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

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

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

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

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

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

Anticarcinogenesis/Antitumorigenesis

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

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

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

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

Radiation Coeffects

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

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

Inhibition of Nitrosamine Formation

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

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

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

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

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

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

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

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

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

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

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

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

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

Inhibition of Developmental and Reproductive Toxicity

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

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

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

CLINICAL ASSESSMENT OF SAFETY

Irritation and Sensitization

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

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

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

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

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

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

Photosensitivity/Phototoxicity

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

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

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

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

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

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

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

[a]RIPT, repeat-insult patch test.

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

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

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

TABLE 8
Clinical photosensitivity/phototoxicity of Propyl Gallate

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

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

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

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

Case Reports

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY

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

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

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

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

CONCLUSION

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

REFERENCES

Abdo, K. M., J. E. Huff, J. K. Haseman, and C. J. Alden. 1986. No evidence of carcinogenicity of d-mannitol and propyl gallate in F344 rats or B6C3F1 mice. *Food Chem. Toxic*ol. 24:1091–1097.

Afanas'ev, G. G., et al. 1968. Enhancement of radiation by antioxidants. *Izv. Akad. Nauk SSSR Ser. Biol.* (3):333–344.

Agatova, A. I., and N. M. Emanuel. 1966. The effect of propyl gallate on SH- and SS-containing enzymes. *Biokhimiya (Moscow)* 31:299–305.

Andrews, F. A., W. H. Beggs, and G. A. Sarosi. 1977. Influence of antioxidants on the bioactivity of amphotericin B. *Antimicrob. Agents Chemother.* 11:615–618.

Association of Public Analysts (APA). 1963. The detection and determination of antioxidants in food. *Spec. Rep.* 1:8.

Ashby J., D. A. Basketter, D. Paton, et al. 1995. Structure activity relationships in skin sensitization using the murine local lymph node assay. *Toxicology* 103:177–194.

Astill, B. D., and T. Mulligan. 1977. Phenolic antioxidants and the inhibition of dimethylamine-nitrite-induced hepatotoxicity in the rat. *Toxicol. Appl. Pharmacol.* 41:163–164.

Athavale, N. V., and C. R. Srinivas. 1994. Contact cheilitis from propyl gallate in lipstick. *Contact Dermatitis* 30:307.

Autrup, H., and G. P. Warwick. 1975. Characteristics of two azoreductase systems in rat liver. *Chem. Biol. Interact.* 11:329–342.

Bajaj I., K. K., et al. 1970. Separation of alkyl gallates as complexes with cinchonine and strychnine. *J. Chromatogr.* 46:261–266.

Balsam, M. S., and E. Sagarin (eds.). 1974. *Cosmetics: Science and technology*, 2nd ed. New York: John Wiley & Sons.

Beggs, W.H., F. A. Andrews, and G. A. Sarosi. 1978. Antioxidant enhancement of amphotericin B activity against *Candida albicans*. *Res. Commun. Chem. Pathol. Pharmacol.* 20:409–412.

Ben-Hur, E., et al. 1981. Differential protective effects of antioxidants against cell killing and mutagenesis of Salmonella typhimurium by gamma radiation. *J. Radiat. Res. (Tokyo)* 22:250–257.

Bentz, R. W., T. J. O'Grady, and S. B. Wright. 1952. Antioxidants and food preservation. *Food Technol.* 6:302–304.

Berger, K. G., et al. 1960. Die Bestimmung Chemischer antioxydantien in Fetten nach Abtrennung durch Verteilungschromatographie. *Analyst* 85:341–346.

Bettger, W. J., and R. G. Ham. 1981. Effects of nonsteroidal anti-inflammatory agents and antioxidants on the clonal growth of human diploid fibroblasts. *Prog. Lipid Res.* 20:265–268.

Blalock, J. E., D. L. Archer, and H. M. Johnson. 1981. Anticellular and immunosuppressive activities of food-borne phenolic compounds. *Proc. Soc. Exp. Biol. Med.* 167:391–393.

Boehm, E., and R. Williams. 1943. A study of the inhibiting actions of propyl gallate (normal propyl trihydroxy benzoate) and certain other trihydric phenols on the autoxidation of animal and vegetable oils. *Q. J. Pharm. Pharmacol.* 16:232–243.

Bojs, G., B. Nicklasson, and Å. Svesson. 1987. Allergic contact dermatitis to propyl gallate. *Contact Dermatitis* 17:294–298.

Booth, A. N., et al. 1959. Die Umwandlung von Gallussaure und verwandten Verbindungen im Stoffwechsel. *J. Biol. Chem.* 234:3014–3016.

Boyd, I., and E. G. Beveridge. 1979. Relationship between the antibacterial activity towards *Escherichia coli* NCTC 5933 and the physico-chemical properties of some esters of 3,4,5-trihydroxybenzoic acid (gallic acid). *Microbioscopy* 24:173–184.

Brzhevskaya, O. N., L. P. Kayushin, and O. S. Nedelina. 1966. Existence of free radicals during enzymic hydrolysis of ATP. *Biofizika* 11:213–216.

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

Carpenter, M. P. 1981. Antioxidant effects on the prostaglandin endoperoxide synthetase product profile. *Fed. Proc.* 40:189–194.

Chatt, E. M. 1962. A survey of methods for the detection and determination of antioxidants in fats and foods. British Food Manufacturing Industries Research Association Techical Circulation No. 206:45. Leatherhead, Surrey, England: BEMIRA.

Chiang, H., and Tseng, R. 1969. Polyamide-kieselguhr thin layer chromatography of antioxidants. *J. Pharm. Sci.* 58:1552–1553.

Chung, K.-T., Z. Lu, and M. W. Chou. 1998. Mechanisms of inhibition of tannic acid and related compounds on the growth of intestinal bacteria. *Food Chem. Toxicol.* 36:1053–1060.

Corazza, M., L. Mantovani, C. Roveggio, and A. Virgili. 1994. Allergic contact dermatitis from propyl gallate. *Contact Dermatitis* 31:203–204.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 1972. *Cosmetic ingredient specifications.* Washington, DC: CTFA.

CTFA. 1976. Acute oral toxicity study of a sun protection stick containing propyl gallate. Unpublished data submitted by CTFA, December 21, 1976.[2]

CTFA. 1977a. Primary skin irritation test on a suntan butter containing propyl gallate. Unpublished data submitted by CTFA, April 14, 1977.[2]

CTFA. 1977b. Acute oral toxicity test on a suntan butter containing propyl gallate. Unpublished data submitted by CTFA, June 15, 1977.[2]

CTFA. 1977c. Acute eye irritation study of a sun protection stick containing propyl gallate. Unpublished data submitted by CTFA, January 18, 1977.[2]

CTFA. 1977d. Acute eye irritation test on a suntan butter containing propyl gallate. Unpublished data submitted by CTFA, May 11, 1977.[2]

CTFA. 1977e. Phototoxicity test on a sun protection stick containing propyl gallate. Unpublished data submitted by CTFA, September 27, 1977.[2]

CTFA. 1977f. RIPT on a suntan butter containing propyl gallate. Unpublished data submitted by CTFA, June 20, 1977.[2]

CTFA. 1977g. Repeat insult patch test on a sun protection stick containing propyl gallate. Unpublished data submitted by CTFA, March 1, 1977.[2]

CTFA. 1977h. Photocontact allergy test on a sun protection stick containing propyl gallate. Unpublished data submitted by CTFA, February 28, 1977.[2]

CTFA 1977i. Phototoxicity test on a sun protection stick containing propyl gallate. Unpublished data submitted by CTFA, February 28, 1977.[2]

CTFA. 1980a. Primary skin irritation and corrosivity study of a lipstick containing propyl gallate (2-8-8). Unpublished data submitted by CTFA, August 7, 1980.[2]

CTFA. 1980b. Primary skin irritation test on a suntan oil containing propyl gallate. Unpublished data submitted by CTFA, June 19, 1980.[2]

CTFA. 1980c. Acute eye irritation study of a lipstick containing propyl gallate (2-8-5). Unpublished data submitted by CTFA, August 7, 1980.[2]

CTFA. 1980d. Acute oral toxicity study of a lipstick containing propyl gallate (2-8-6). Unpublished data submitted by CTFA, August 7, 1980.[2]

CTFA. 1980e. Repeated insult patch test (RIPT) of a lipstick containing propyl gallate (2-8-7). Unpublished data submitted by CTFA, October 2, 1980.[2]

CTFA. 1980f. RIPT on a suntan oil containing propyl gallate. Unpublished data submitted by CTFA, September 12, 1980.[2]

CTFA. 1980g. Controlled use test on a suntan oil containing propyl gallate. Unpublished data submitted by CTFA, September 25, 1980.[2]

[2]Available for review from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 412, Washington, D.C. 20036, USA.

CTFA. 1981a. Acute eye irritation test on three cosmetic formulations containing propyl gallate. Unpublished data submitted by CTFA, November 9, 1981.[2]

CTFA. 1981b. Acute eye irritation test on three cosmetic formulations containing propyl gallate. Unpublished data submitted by CTFA, November 17, 1981.[2]

CTFA. 2003. Concentration of use of Propyl Gallate in cosmetic products. Unpublished data submitted by CTFA.[2]

Cusano, F., M. Capozzi, and G. Errico. 1987. Safety of propyl gallate in topical products. *J. Am. Acad. Dermatol.* 17:308–309.

Dacre, J. C. 1960. Metabolic pathways of the phenolic antioxidants. *J. N. Z. Inst. Chem.* 24:161–171.

Dacre, J. C. 1974. Long-term toxicity study of n-propyl gallate in mice. *Food Cosmet. Toxicol.* 12:125–129.

Daniialov, M. A. 1966. Hygienic assessment of a mixture containing antioxidants of alimentary fats: butylhydroxyanisole and propyl gallate. *Vopr. Pitan.* 25:47–51.

Davidek, J., and J. Pokorny 1961. Detection of antioxidants in fats with the aid of thin-layer chromatography on polyamide powder. *Z. Lebensm. Untersuch. Forsch.* 115:113–117.

Desesso, J. M. 1981. Amelioration of teratogenesis: I. Modification of hydroxyurea-induced teratogenesis by the antioxidant propyl gallate. *Teratology* 24:19–35.

Dessel, L. Van, and J. Clement. 1969. Thin-layer chromatographic separation of antioxidants (in fats and oils). *Z. Lebensm. Unters. Forsch.* 139:146–149.

Dianzani, M. U. 1972. Liver steatosis induced by white phosphorus. *Morgagni* 5:1–23.

Dianzani, M. U., and G. Ugazio. 1973. Lipoperoxidation after carbon tetrachloride poisoning in rats previously treated with antioxidants. *Chem. Biol. Interact.* 6:67–79.

Draize, J. H. 1959. Dermal toxicity in appraisal of the safety of chemicals. In: *Foods, Drugs and Cosmetics*, 46–59. Division of Pharmacology, FDA, Dept. of HEW Assoc. of Food and Drug Officials of the US Business Office, Bureau of Food and Drugs, Austin, Texas.

Elder, R. L., ed.1985. Final report on the safety assessment of Propyl Gallate. *J. Am. Col. Toxicol.* 4:23–64.

Emanuel, N. M., L.P. Lipchina, and I.I. Pelevina. 1959. Selective lowering of the RNA content of tumor cells and their loss of implantability after treatment in vitro with inhibitors of chain reactions. *Dokl. Biochem.* 125:89–92.

Emanuel, N. M., et al. 1976. Suppression of RNA synthesis by propyl gallate in the RNA-polymerase system. *Izv. Akad. Nauk SSSR Ser. Biol.* 4:517–519.

Ershoff, B. H., and C. W. Steers, Jr. 1960. Antioxidants and survival time of mice exposed to multiple sublethal doses of x-irradiation. *Proc. Soc. Exp. Biol. Med.* 104:274–276.

FAO/WHO Expert Committee on Food Additives. 1965. *Specifications for identity and purity and toxicological evaluation of some antimicrobials and antioxidants.* WHO/Food Add./24.65; FAO Nutr. Meet. Rep. Ser. No. 38A.

Feuer, G., et al. 1965. Liver response tests. VI. Application to a comparative study of food antioxidants and hepatotoxic agents. *Food Cosmet. Toxicol.* 3:457–469.

Fiss I. and E. Wagner 1988. Allergic contact eczema by propyl gallate. *Dermatol. Monatsschr.* 174:14–19.

Food and Drug Administration (FDA). 2002. Reported uses of Propyl Gallate in cosmetic product formulations. *FDA database*. Washington, DC: FDA.

Food and Drugs Research Labs (FDRL). 1972. GRAS (Generally Recognized As Safe) food ingredients: Propyl gallate. (PB-221 207):1–51.[2]

FDRL. 1972b. Teratologic evaluation of FDA 71-39 (propyl gallate). (PB-221 790):1–42 .[2]

FDRL. 1973. Teratologic evaluation of FDA 71-39 (propyl gallate). (PB-223 816):1–14.[2]

FDRL. 1981a. Clinical safety evaluation (photoallergy series) of sunscreen formulation: SP-104-L-3A. (July 31, 1981).[2]

FDRL. 1981b. Clinical safety evaluation (photoallergy series) of sunscreen formulation: SP-104-L-3B. (July 31, 1981).[2]

FDRL. 1981c. Clinical safety evaluation (photoallergy series) of sunscreen formulation: SP-104-L-5. (December 3, 1981).[2]

FDRL. 1981d. Clinical safety evaluation (photoallergy series) of sunscreen formulation: SP-107-1. (December 31, 1981).[2]

FDRL. 1981e. Clinical safety evaluation (photoallergy series) of sunscreen formulation: SP-107-4. (December 31, 1981).[2]

FDRL. 1981f. Clinical safety evaluation (photoallergy series) of sample: SP-103-3-A, a cosmetic formulation containing propyl gallate. (July 2, 1981).[2]

FDRL. 1981g. Clinical safety evaluation (photoallergy series) of sample: SP-103-3-E, a cosmetic formulation containing propyl gallate. (July 2, 1981).[2]

Forgo, I., and J. Buchi. 1970. Synthesis, physical-chemical properties and antioxidative effect of some gallic acid esters. I. Nature, mechanism of action and properties of antioxidants. *Pharm. Acta Helv.* 45:207–226.

Franzone, J. S., et al. 1980. Effect of propyl gallate and 2-mercaptopropionyl glycine on the development of acute inflammatory reactions and on PGE_2 biosynthesis. *Boll. Soc. Ital. Sper.* 56:2539–2545.

Fukuhara, Y., D. Yoshida, and F. Goto. 1981. Reduction of mutagenic products in the presence of polyphenols during pyrolysis of protein. *Agric. Biol. Chem.* 45:1061–1066.

Gellin, G. A., et al. 1979. Detection of environmental depigmenting substances. *Contact Dermatitis* 5:201–213.

Gonikberg, E. M., et al. 1967. Complex formation in the flavin mononucleotide-H–propylgallate system. *Biofizika* 12:814–819.

Gorodetskii, A. A., V. A. Baraboi, and V. P. Chernetskii. 1961. Protective action of some inhibitors of the chain oxidative processes during the acute radiation syndrome. *Radiobiologiya* 1:781–788.

Gottschalck, T. E., and G. N. McEwen, Jr. eds. 2004. *International Cosmetic Ingredient Dictionary and Handbook*, 10th ed. Washington, DC: CTFA.

Graham, W.D., and H. C. Grice. 1955. Chronic toxicity of bread additives to rats. II. *J. Pharm. Pharmacol.* 7:126–134.

Graham, W. D., H. Teed, and H. C. Grice. 1954. Chronic toxicity of bread additives to rats. *J. Pharm. Pharmacol.* 6:534–545.

Gravela, E., L. Gabriel, and G. Ugazio. 1971. Protection by glutathione and propyl gallate on the impaired in vitro amino acid incorporation into liver microsomal protein of carbon tetrachloride-poisoned rats. *Biochem. Pharmacol.* 20:2065–2070.

Gutteridge, J. M., and K. C. Fu. 1981. Enhancement of bleomycin-iron free radical damage to DNA by antioxidants and their inhibition of lipid peroxidation. *FEBS Lett.* 123:71–74.

Hausen, B. M., and W. Beyer. 1992. The sensitization capacity of the antioxidants propyl, octyl, and dodecyl gallate and some related gallic acid esters. *Contact Dermatitis* 26: 253–258.

Heine, A. 1988. Contact dermatitis from propyl gallate. *Contact Dermatitis* 18: 313–314.

Hemmer, W., et al. 1996. Group allergy to tri- and ortho-diphenols (catechols) in a patient sensitized by propyl gallate. *Contact Dermatitis* 35: 110–112.

Hernandez, N., H. Assier-Bonnet, N. Terki, and J. Revuz. 1997. Allergic contact dermatitis from propyl gallate in desonide cream (Locapred). *Contact Dermatitis* 36:111.

Hill Top Research. 1978. Unpublished study of cumulative irritant properties of test materials, (2-8-2). Unpublished data submitted by CTFA, January 5, 1978.[2]

Ichihara, K., et al. 1979. Fatty acid activation of guanylate cyclase from fibroblasts and liver. *Arch. Biochem. Biophys.* 197:44–51.

Ishidate, M. J., et al. 1978. Cytotoxicity test on medical drugs. Chromosome aberration tests with Chinese hamster cells in vitro. *Eisei Shikensho Hokoku* 96:55–61.

Isupova, L. S., and V. S. Balabukha. 1963. Prevention of radiation-induced depolymerization of deoxyribonucleic acid (DNA) of rat liver by means of propyl gallate and 5-methoxy-tryptamine. *Radiobiologiya* 3:256–258.

Japan Cosmetic Industry Association (JCIA). 1979. *Japanese Standards of Cosmetic Ingredients*. Tokyo: Yakuji Nippo.

Johnson, F. C. 1971. A critical review of the safety of phenolic antioxidants in foods. In: *CRC Critical Review of Food Technology.* Boca Raton, FL: CRC Press.

Johnson, A. R., and F. R. Hewgill. 1961. The effect of the antioxidants, butylated hydroxyanisole, butylated hydroxy toluene and propyl gallate on growth, liver and serum lipids and serum sodium levels of the rat. *Aust. J. Exp. Biol. Med. Sci.* 39:353–360.

Jordan, H. V., A. E. Bowler, and N. D. Berger. 1961. Testing of antioxidants against experimental caries in rats. *J. Dental Res.* 40:878–883.

Kahn, G., and M. C. Curry. 1974. Ultraviolet light protection by several new compounds. *Arch. Dermatol.* 109:510–517.

Kahn, G., M. C. Curry, and R. Dustin. 1973. New approaches to investigating UVL (ultraviolet light) photoprotective substances in vitro. *Arch. Dermatol. Forsch.* 246:301–318

Kahn, G., P. Phanuphak, and H.N. Claman. 1974. Propyl gallate contact sensitization and orally-induced tolerance. *Arch. Dermatol.* 109:506–509.

Karplyuk, I. A. 1959. Toxicologic characteristics of phenolic antioxidants of edible fats. *Voprosy Pitaniya* 18:24–29.

Karplyuk, I. A. 1968. Study of the enzyme secretory function of the small intestine and pancreas mucosa in rats fed a diet containing phenol antioxidants. *Vopr. Pitan.* 27:21–26.

Kawachi, T., et al. 1980. Cooperative program on short-term assays for carcinogenicity in Japan. *IARC (Int. Agency Res. Cancer) Sci. Publ.* 27:323–330.

Kawanishi, T., et al. 1981. Studies on nitrosamine formation by the interaction between drugs and nitrite. I. Measurement of the amount of nitrosamine formed in rat and guinea pig stomachs. *J. Toxicol. Sci.* 6:261–286.

Kelleher, J., et al. 1976. Modification of paracetamol toxicity by antioxidants. *Biochem. Soc. Trans.* 4:292–294.

King, D. W. 1964. Comparative effects of certain antioxidants on gestational performance and teratogeny in vitamin E deficient rats. *J. Nutr.* 83:123–132.

King, M. M., and P. B. McCay. 1981. Studies on liver microsomes of female rats fed purified diets varying in fat content and with and without propyl gallate. *Food Cosmet. Toxicol.* 19:13–18.

King, W. P., K. T. Joseph, and P. T. Kissinger. 1980. Liquid chromatography with amperometric detection for determining phenolic preservatives. J. *Assoc. Off. Anal. Chem*, 63:137–142.

Kline, D. A., F. L. Joe, Jr., and T. Fazio. 1978. A rapid gas-liquid chromatographic method for the multideterminationof antioxidants in fats, oils, and dried food products. *J. Assoc. Off. Anal. Chem.* 61:513–519.

Kozumbo, W. J., J. L. Seed, and T. W. Kensler. 1982. Antioxidants: Potent inhibitors of 12-*o*-tetradecanoyl phorbol-13-acetate (TPA)-induced ornithine decarboxylase (ODC) activity in mouse epidermis. *Proc. Am. Assoc. Cancer Res.* 23:395.

Kraus, A. L., J. Stotts, L. A. Altringer, and G. S. Allgood. 1990. Allergic contact dermatitis from propyl gallate: dose response comparison using various application methods. *Contact Dermatitis* 22:132–136.

Kubo, I., K. Fujita, and K. Nihei. 2002. Anti-*Salmonella* activity of alkyl gallates. *J. Agric. Food Chem.* 50: 6692–6696.

Kukushkina, G. V., L. B. Gorbacheva, and N. M. Emanuel. 1966a. Inhibition of protein and nucleic acid biosynthesis by phenols in vivo. *Vopr. Med. Khim.* 12:452–455.

Kukushkina, G. V., L. B. Gorbacheva, and N. M. Emanuel. 1966b. Effect of phenolic compounds on the biosynthesis of protein and nucleic acids in cells of human laryngeal cancer Hep-2. *Vopr. Onkol.* 12:54–56.

Lake, B. G., et al. 1980. The effect of treatment with some phase II substrates on hepatic xenobiotic metabolism and the urinary excretion of metabolites of the D-glucuronic acid pathway in the rat. *Toxicol. Appl. Pharmacol.* 52:371–378.

Law, E., and A. J. Lewis. 1977. The effect of systemically and topically applied drugs on ultraviolet-induced erythema in the rat. *Br. J. Pharmacol.* 59:591–597.

Latz, H. W., and R. J. Hurtubise. 1969. Luminescence analysis of food antioxidants; determination of propyl gallate in lard. *J. Agr. Food Chem.* 17:352–355.

Lehman, A. J. 1950. Some toxicological reasons why certain chemicals may or may not be permitted as food additives. *Assoc. Food Drug Officials U. S. Q. Bull.* 14:82–98.

Lehman, A. J. et al. 1951. Pharmacological evaluation of antioxidants. *Adv. Food Res.* 3:200.

Levitt, M., et al. 1967. A new class of tyrosine hydroxylase inhibitors and a simple assay of inhibition in vivo. *Biochem Pharmacol.* 16:1313–1321.

Lewis, R. J., Sr. 1997. *Hawley's Condensed Chemical Dictionary*, 935. New York: John Wiley & Sons.

Life Sciences Research Office (LSRO). 1973. Evaluation of the health aspects of propyl gallate as a food ingredient. (PB-223 840):1–13.

Lipchina, L. P., et al.1960. Suppression of mitosis in a culture of human cancer cells by inhibitors of free radical reactions. *Dokl. Akad. Nauk SSSR* 131:667–669.

Lipkan, M. F., V. A. Baraboi, and R.G. Lukashova. 1962. Nucleic acids in rat organs and the effects of roentgen radiation and propyl gallate. *Ukr. Biokhim. Zh.* 34:167–175.

Lisanti, V. F., and B. Eichel. 1963. Antioxidant inhibition of experimentally induced caries in hamsters. *J. Dent. Res.* 42:1030–1035.

Litton Bionetics. 1974. Mutagenic evaluation of compound FDA 71-39, propyl gallate. (PB-245 441):1–138.

Lo, L. W., and H. F. Stitch. 1978. The use of short-term tests to measure the preventive action of reducing agents on formation and activation of carcinogenic nitroso compounds. *Mutat. Res.* 57:57–67.

Mahendran R., R. M. Quinlan, and S. M. Wilkinson. 2002. Allergic contact dermatitis from occupational propyl gallate exposure. *Contact Dermatitis* 47:122–123.

Marks, J. G., Jr., P. Elsner, and V. DeLeo. 2002. *Contact Occupational Dermatology*, 3rd ed., 166. St. Louis: Mosby.

Marston, S. 1992. Propyl gallate on liposomes. *Contact Dermatitis* 27: 74–76.

Matthew, T. V., and S. N. Mitra. 1965. Separation and identification of antioxidants in oils and fats by thin-layer chromatography. *Indian J. Technol.* 3:102.

McCaulley, D. F., et al. 1967. The multidetermination of antioxidants in lard. *J. Assoc. Off. Anal. Chem.* 50:243–250.

McCay, P. B., M. M. King, and J. V. Pitha. 1981. Evidence that the effectiveness of antioxidants as inhibitors of 7,12-dimethylbenz[a]anthracene-induced mammary tumors is a function of dietary fat composition. *Cancer Res.* 41:3745–3747.

McDonald-Gibson, W. J., and C. Schneider. 1974. A novel method for evaluating antiinflammatory drugs in the conscious guinea pig. *Br. J. Pharmacol.* 52:1–149.

McDonald-Gibson, W. J., S. A. Saeed, and C. Schneider. 1976. The local antinociceptive and topical anti-inflammatory effects of propyl gallate in rodents. *Br. J. Pharmacol.* 58:573–581.

Miguez, M., et al. 2003. Alternative oxidase reduces the sensitivity of *Mycosphaerella graminicola* to QOI fungicides. *Pest Manag. Sci.* 60:3–7.

Mitchell, L. C. 1957. Separation and identification of four antioxidants, butylated hydroxyanisole, butylated hydroxytoluene, n-propyl gallate, and nordihydroguaiaretic acid by paper chromatography. *J. Assoc. Off. Anal. Chem.* 40:909–915.

Modak, A. T., and Rao, M. R. 1971. Propyl gallate as a local anesthetic agent. *Indian J. Med. Res.* 59:795–798.

National Toxicology Program (NTP). December 1982. Carcinogenesis bioassay for propyl gallate in F344 rats and B63CF1 mice. NTP-81-42, NIH Publication No. 83–1796.

Neifakh, E. A. 1962. Specific inhibition of activity of reduction-oxidation enzymes of glycolysis of inhibitors of free-radical reactions. *Dokl. Akad. Nauk SSSR* 142:1405–1408.

Nitzan, M., B. Volovitz., and E. Topper. 1979. Infantile methemoglobinemia caused by food additives. *Clin. Toxicol.* 15:273–280.

Nugteren, D. H., et al. 1966. The enzymic conversion of all-*cis*-8,11,14-eicosatrienoic acid into prostaglandin E. *Rec. Trav. Chem.* 85:405–419.

Odintosva, S. P., and K. E. Kruglyakova, 1976. Dual nature of effect of propyl gallate on DNA subjected to irradiation. *Dokl. Biophys. USA* 226-228:9–12.

Omaye, S. T., K. A. Reddy, and C. E. Cross. 1977. Effect of butylated hydroxytoluene and other anti-oxidants on mouse lung metabolism. *J. Toxicol. Environ. Health* 3:829–836.

Orten J. M., et al. 1948. Studies on the toxicity of propyl gallate and of antioxidant mixtures containing propyl gallate. *Food Technol.* 2:308–316.

Page, B. D. 1979. High performance liquid chromatographic determination of nine phenolic antioxidants in oils, lards, and shortenings, J. *Assoc. Off. Anal. Chem*. 62:1239–1246.

Page, B. D., and B. P. C. Kennedy. 1976. Rapid determination of butylated hydroxyanisole, tert-butylhydroquinone, and propyl gallate in edible oils by electron capture gas-liquid chromatography. *J. Assoc. Off. Anal. Chem*. 59:1208–1212.

Panganamala, R. V., et al. 1977. Differential inhibitory effects of vitamin E and other antioxidants on prostaglandin synthetase, platelet aggregation and lipoxidase. *Prostaglandins* 14:261–271.

Pani, P., et al. 1972. Mechanism of fatty liver in white phosphorus poisoned rats. *Exp. Mol. Pathol*. 16:201–209.

Paradisi, L., et al. 1979. Interference of antioxidants and/or of some free radical scavengers: with the activity of glucose-6-phosphatase after administration of carbon tetrachloride. *Boll. Soc. Ital. Biol. Sper*. 55:1877–1883.

Parkhomenko, I. M. 1963. Effect of some radioprotectors under g-irradiation of the cells of cynomolgus monkey heart in vitro. *Radiobiologiya* 3:467–471.

Posati, L. P., K. K. Fox, and M. J. Pallansch. 1970. Inhibition of bradykinin by gallates. *J. Agric. Food Chem.* 18:632–635.

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

Rao, G. S., J. C. Osborn, and M. R. Adatia 1982. Drug-nitrite interactions in human saliva: Effects of food constituents on carcinogenic n-nitrosamine formation. *J. Dent. Res*. 61:768–771.

Registry of Toxic Effects of Chemical Substances (RTECS). 2004. Propyl gallate entry. *RTECS Database*. Bethesda, MD: National Library of Medicine.

Retico, A., N. Simonett, and A. Tornsantucci. 1981. Effect of propyl gallate on antibacterial activity of meclocycline sulfosalicyclate. *Il Farmco* 36: 817–826.

Riley, P. A., and P. Seal. 1974. The role of substituted anisoles in epidermal microinvasion. *J. Pathol*. 114:1–7.

Rizzuto, F., and J. D. Spikes. 1975. Mechanisms involved in the chemical inhibition of the eosin-sensitized photooxidation of trypsin. *Radiat. Environ. Biophys*. 12:217–232.

Rosin, M. P., and H. F. Stich. 1979. Assessment of the use of the *Salmonella mutagenesis* assay to determine the influence of antioxidants on carcinogen-induced mutagenesis. *Int. J. Cancer* 23:722–727.

Rosin, M. P., and H. F. Stich. 1980. Enhancing and inhibiting effects of propyl gallate on carcinogen-induced mutagenesis. *J. Environ. Pathol. Toxicol*. 4:159–168.

Rothwell, S. W. 2003. Addition of a propyl gallate-based procoagulant to a fibrin bandage improves hemostatic performance in a swine arterial bleeding model. *Thrombosis Res*. 108:335–340.

Sasaki, M., et al. 1980. Cytogenetic effects of 60 chemicals on cultured human and Chinese hamster cells. *Senshokutai* 20:574–584.

Schuh, J., G. F. Fairclough, JR., and R. H. Haschemeryer. 1978. Oxygen-mediated heterogeneity of apo-low-density lipoprotein. *Proc. Natl. Acad. Sci. U. S. A*. 75:3173–3177.

Sen, N. P., et al. 1976. Inhibition of nitrosamine formation in fried bacon by propyl gallate and L-ascorbyl palmitate. *J. Agr. Food Chem*. 24:397–401.

Shelef, L. A., and Chin, B. 1980. Effect of phenolic antioxidants on the mutagenicity of aflatoxin B2. *Appl. Environ. Microbiol*. 40:1039–1043.

Sheng, P., H. Wang, and Z. Shen. 1982. Transfer of radiation-induced spins from deoxyribonucleic and thymidylic acids to Propyl Gallate. *Sci. Sin. (Engl. Ed.)* 25:473–484.

Shih, A. L., and N. D. Harris. 1977. Antimicrobial activity of selected antioxidants. *J. Food Prot*. 40:520–522.

Sietsema, W. K., and H. F. DeLuca. 1979. In vitro epoxidation of all-*trans*-retinoic acid in rat tissue homogenates. *Biochem. Biophys. Res. Commun*. 90:1091–1097.

Simmon, V. F., and S. L. Eckford. 1978. Microbial mutagenesis testing of substances. Compound report: F76-Q12, propyl gallate. Report (L5U-6909):14.[2]

Slater, T. F., and B. C. Sawyer. 1971. Stimulatory effects of carbon tetrachloride on peroxidative reactions in rat liver fractions in vitro. Inhibitory effects of free-radical scavengers and other agents. *Biochem. J*. 123:823–828.

Spingarn, N. E, and C. T. Garvie. 1979. Formation of mutagens in sugar-ammonia model systems. *J. Agric. Food Chem*. 27:1319–1321.

Spirichev, V. B., and N. V. Blazhevich. 1968. The hemolytic action of vitamin D2. Formation of lipoperoxides. *Vopr. Med. Khim*. 14:371–375.

Stillmeadow. 1977a. Acute oral toxicity study in rats of a lipstick containing Propyl Gallate (2-8-3). Unpublished data submitted by CTFA, November 29, 1977.[2]

Stillmeadow. 1977b. Acute oral toxicity study in rats of a lipstick containing propyl gallate (2-8-4). Unpublished data submitted by CTFA, November 29, 1977.[2]

Stoner, G. D., et al. 1973. Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A mice. *Cancer Res*. 33:3069–3085.

Tanaka, S., et al. 1979. Effect of dietary administration of propyl gallate during pregnancy on prenatal and postnatal developments of rats. *Shokuhin Eiseigaku Zasshi* 20:378–384.

Tarjan, R., et al. 1965. Effects produced on warm-blooded animals by admixtures and adjuvants contained in foodstuffs of Hungarian origin. *Vopr. Pitan*. 24:11–17.

Telford, I. R., C. S. Woodruff, and R. H. Linford. 1962. Fetal resorption in the rat as influenced by certain antioxidants. *Am. J. Anat*. 110:29–36.

Thompson, D. T., J. J. Vogel, and P. H. Phillips. 1965. Certain organic substances and their effects on the incidence of dental caries in the cotton rat. *J. Dent. Res*. 44:596–599.

To, D., F. L. Smith, and M. P. Carpenter. 1980. Mammary gland prostaglandin synthesis: Effect of dietary lipid and propyl gallate. Adv. *Prostaglandin Thromboxane Res*. 8:1807–1812.

Torrielli, M. V., and T. E. Slater. 1971. Inhibition of NADPH-cytochrome *c* reductase by propyl gallate. *Biochem. Pharmacol*. 20:2027–2032.

Torrielli, M. V., and G. Ugazio. 1975. Biochemical aspects of the protective action of propyl gallate on liver injury in rats poisoned with carbon tetrachloride. *Toxicol. Appl. Pharmacol*. 34:151–169.

Ugazio, G., and M. V. Torrielli. 1968. Effect of propyl gallate on hepatic steatosis induced by carbon tetrachloride. *Boll. Soc. Ital. Biol. Sper*. 44:1166–1170.

Valsecchi, R., and T. Cainelli. 1988. Contact allergy to propyl gallate. *Contact Dermatitis* 19:380–381.

Wachs, W., and Gassmann, L. 1970. Determination of gallic acid esters by gas chromatography. *Deutsch. Lebensm. Rundsch*. 66:37–38.

Wan, L. S. C. 1972. Solubilization of gallates in solutions of nonionic surfactants. *Can. J. Pharm. Sci*. 7:25–27.

Weast, R. C., (ed.). 1978. *Handbook of Chemistry and Physics*, 59th ed. Boca Raton, FL: CRC Press.

Wilkinson, S. M., and M. H. Beck. 1992. Allergic contact dermatitis from dibutyl phthalate, propyl gallate and hydrocortisone in Timodine. *Contact Dermatitis* 25:197.

Williams, D. S., and T. F. Slater. 1973. Photosensitization of isolated lysosomes. *Biochem. Soc. Trans*. 1:200–202.

Wilson, A. G. McT., I. R. White, and J. D. T. Kirby. 1989. Allergic contact dermatitis from propyl gallate in a lip balm. *Contact Dermatitis* 20:145–146.

Windholz, M., (ed.). 1976. *The Merck Index*, 9th ed. Rahway, NJ: Merck & Co.

Vartanyan, L. S., E. M. Gonikberg, and N. M. Emanuel. 1964. Kinetics of lactic dehydrogenase inactivation with free-radical products of propyl gallate autoxidation. *Izv. Akad. Nauk SSSR Ser. Khim*. 10:1742–1748.

Van Esch, G. J. 1955. The toxicity of the antioxidants propyl-, octyl-, and dodecylgallate. *Voeding* 16:683–686.

Yang, C. S., and F. S. Strickhart. 1974. Inhibition of hepatic mixed function oxidase activity by propyl gallate. *Biochem. Pharmacol*. 23:3129–3138.