Amended Safety Assessment of Alkyl Gallates as Used in Cosmetics

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All interested persons are provided 60 days from the above release date (i.e., by June 13, 2026) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

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.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, 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, M.B.A. This safety assessment was prepared by Priya Ferguson, M.S., Senior Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

A549	lung cancer cell line
ADME	absorption, distribution, metabolism, and excretion
B16F10	murine melanoma cell line
C_{max}	peak plasma concentration
C_{max1}	first peak plasma concentration
C_{max2}	second peak plasma concentration
C_{max3}	third peak plasma concentration
CA 15.3	cancer antigen 15.3
Caco-2	colorectal adenoma cell line
Calu-6	lung cancer cell line
CD54	cluster of differentiation 54
CD86	cluster of differentiation 86
CEA	carcinoembryonic antigen
CHO	Chinese hamster ovary
CIR	Cosmetic Ingredient Review
$CLint_{app}$	apparent intrinsic clearance
CMC	carboxymethylcellulose
Council	Personal Care Products Council
Dictionary	*International Cosmetic Ingredient Dictionary*
DMBA	dimethylbenzanthracene
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DNCB	dinitrochlorobenzene
ECHA	European Chemicals Agency
ER	estrogen receptor
FDA	Food and Drug Administration
GD	gestation day
GRAS	generally recognized as safe
GV	germinal vesicle
HepG2	human liver cell line
^{3}HTdR	[^{3}H]methyl thymidine
IC_{50}	half-maximal inhibitory concentration
IL-18	interleukin-18
INCI	International Nomenclature of Cosmetic Ingredients
IVIS	in vitro irritation score
JEFCA	Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives
K_i	binding affinity
LD_{50}	median lethal dose
LEC	lowest effect concentration
LLNA	local lymph node assay
l.o.	leave-on
log K_{ow}	octanol-water partition coefficient
MG-63	human osteosarcoma cell line
MCF-7	breast cancer cell line
MoCRA	Modernization of Cosmetics Regulation Act of 2022
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
mRNA	messenger ribonucleic acid
NA	not applicable
NACDG	North American Contact Dermatitis Group
NOAEL	no-observed-adverse-effect-level
4-NQO	4-nitroquinoline-1-oxide
NR	not reported
OECD	Organisation for Economic Cooperation and Development
P_{app}	apparent permeability coefficient
Panel	Expert Panel for Cosmetic Ingredient Safety
PBE	polar body extrusion
PBK	physiologically-based kinetic

PMA	phorbol-12-myristate-13-acetate
RLD	Registration and Listing Data
RNA	ribonucleic acid
r.o.	rinse-off
SCE	sister chromatid exchange
SI	stimulation index
T47D-Kbluc	T47D breast cancer cells with estrogen response element luciferase reporter
$T_{1/2}$	half-life
THP-1	human monocytic leukemia cell line
T_{max}	time to reach peak plasma concentration
T_{max1}	time to reach C_{max1}
T_{max2}	time to reach C_{max2}
T_{max3}	time to reach C_{max3}
TG	test guidelines
U2-OS	human osteosarcoma cell line
U87	human glioblastoma cell line
US	United States
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) reassessed the safety of Propyl Gallate, along with 3 additional structurally-related alkyl gallates that had not been reviewed. All of these ingredients are reported to function as antioxidants in cosmetic formulations. The Panel reviewed all relevant data related to these ingredients. Accordingly, the Panel issued an amended report with a revised conclusion stating that these 4 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating and non-sensitizing.

INTRODUCTION

This assessment reviews the safety of the following 4 ingredients as used in cosmetic formulations:

Caprylyl Gallate	Ethylhexyl Gallate
Dodecyl Gallate	Propyl Gallate

Propyl Gallate has previously been reviewed by the Panel in a safety assessment that was published in 1985.[1] In that report, it was concluded that Propyl Gallate is safe as a cosmetic ingredient at concentrations not exceeding 1%. In 2007, after the review of new data indicating positive patch test results at 0.5% Propyl Gallate, a Final Amended Report was published on Propyl Gallate with the conclusion that Propyl Gallate is safe in the present practices of use as described in that safety assessment at concentrations less than or equal to 0.1%.[2] Because it had been at least 15 years since the Amended Report was published, in accordance CIR Procedures, the Panel reconsidered the safety of Propyl Gallate in June 2024, and determined to re-open this safety assessment due to new toxicity data (e.g., genotoxicity; developmental and reproductive toxicity), and for the inclusion of other in-use alkyl gallates that have not been reviewed by the Panel (i.e., Caprylyl Gallate, Dodecyl Gallate, and Ethylhexyl Gallate).

According to the *International Cosmetic Ingredient Dictionary* (*Dictionary*), Caprylyl Gallate, Dodecyl Gallate, Ethylhexyl Gallate, and Propyl Gallate function as antioxidants in cosmetic formulations (Table 1).[3] Propyl Gallate also functions as a fragrance ingredient. These ingredients have been grouped together as they are structurally-related gallic acid esters.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; a search was last conducted in January 2026. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.[4] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

Excerpts from the summaries of the previous 2007 Final Amended Report on Propyl Gallate are disseminated throughout the text of this document, as appropriate, and are identified by *italicized text*. (This information is not included in the tables or the summary section.). Data from the 1985 report are not summarized separately here, as those data were already included and summarized in the 2007 report.

It should be noted that in most studies referring to Caprylyl Gallate as the test article, the substance identified in the publication was octyl gallate. Because octyl gallate is a technical name for Caprylyl Gallate according to the *Dictionary*, the term Caprylyl Gallate is used throughout the report; however, the designation "octyl-" in the literature may refer to either caprylyl- or 2-ethylhexyl-, and therefore equivalence in these studies should be determined on a case-by-case basis. It should also be noted that based on evidence presented in the literature for the studies included in this document (in non-italicized text), it is reasonable to assume that these studies pertain to Caprylyl Gallate. Additionally, in some cases, lauryl gallate was identified as the test substance in the literature; however, Dodecyl Gallate is used in this report, as it is synonymous with lauryl gallate, and represents the corresponding INCI designation.

CHEMISTRY

Definition and Structure

Caprylyl Gallate (CAS No. 1034-01-1), Dodecyl Gallate (CAS No. 1166-52-5), Ethylhexyl Gallate (CAS No. 34531-26-5), and Propyl Gallate (CAS No. 121-79-9) are alkyl esters of gallic acid (3,4,5-trihydroxybenzoic acid) in which the carboxyl group of gallic acid is esterified with the corresponding alcohol.[5,6] The definitions and structures of the ingredients included in this review are provided in Table 1.

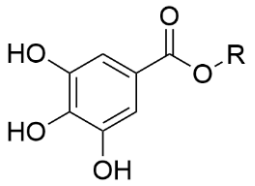


Figure 1. Alkyl gallates, wherein R is a caprylyl, dodecyl, 2-ethylhexyl, or propyl group.

Chemical Properties

Propyl Gallate is a white to light brown, crystalline, odorless powder.[2] The molecular weights and octanol-water partition coefficients (log K_{ow}) of these ingredients range from 212.2 – 338.4 g/mol and 1.80 – 6.75, respectively.[2,7-11] Other chemical properties of the ingredients reviewed in this report may be found in Table 2.

Method of Manufacture

Propyl Gallate

Propyl Gallate may be commercially prepared via esterification of gallic acid with propyl alcohol.[2] *The resulting substance is distilled to remove excess alcohol.*

Impurities

Propyl Gallate

The specifications for Propyl Gallate as a cosmetic ingredient include impurity limits of arsenic (< 3 ppm) and lead (< 20 ppm).[2] *In addition, the ingredient must contain < 0.1% ash.*

Dodecyl Gallate

According to the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives (JECFA), Dodecyl Gallate has a minimum purity of 98.5% on a dried basis.[12] Purity limits include loss on drying ≤ 0.5%, sulfated ash ≤ 0.05%, free acid (as gallic acid) ≤ 0.5%, lead ≤ 2 mg/kg, and chlorinated organic compounds ≤ 100 mg/kg.

Propyl Gallate

According to JECFA, Propyl Gallate is specified to be 98 – 102% pure on a dried basis.[13] Purity limits include loss on drying ≤ 0.5%, sulfated ash (following pyrolization) ≤ 0.1%, free acid (as gallic acid) ≤ 0.5%, lead ≤ 2 mg/kg, and chlorinated organic compounds ≤ 100 mg/kg.

Reactivity

Propyl Gallate

The antioxidant activity of Propyl Gallate is due to hydrogen-donating hydroxyl groups.[2] *This ingredient is stable in in neutral or slightly acidic environments but is unstable when heated or in mild alkaline environments. Propyl Gallate is a free-radical scavenger, preventing lipid peroxidation by reacting with lipid peroxy radicals and stopping the chain reaction that leads to lipid damage.*

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these alkyl gallates in cosmetics. Registration and Listing Data (RLD) obtained from the FDA report frequency of use, and responses to a survey conducted by the Personal Care Products Council (Council) indicate maximum reported concentrations of use; it is these values that define the present practices of use and concentration that are assessed by the Panel. Since 2024, as a result of the Modernization of Cosmetics Regulation Act of 2022 (MoCRA), manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-yr period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products, are not included in this exemption.[14] Another change resulting from MoCRA is the addition of tattoo preparations (permanent tattoo inks, temporary tattoo inks, and other tattoo products) to the product categories for which companies need to list their products with FDA. However, evaluating the safety of ingredients as used in tattoo preparations is not within the purview of the Panel; accordingly, such use is not included as part of the present practices of use that are assessed by the Panel.

According to RLD obtained from the FDA in 2025 and the results of the 2024 Council survey, Propyl Gallate is used in 1127 total formulations, at up to 0.1% (in leave-on face and neck products; Table 3).[15-17] All other ingredients are reported to be used in 21 formulations or less. No concentrations of use were reported for Caprylyl Gallate, Dodecyl Gallate, or Ethylhexyl Gallate.

When determining whether to re-open the safety assessment on Propyl Gallate, the Panel considered FDA Voluntary Cosmetic Registration Program (VCRP) data submitted to CIR in 2023. In 2023, Propyl Gallate was reported to be used in 86 formulations, as opposed to 164 formulations reported in 2002.[2,18] In addition, the reported maximum concentration of use has remained the same; in 2003, the maximum concentration of use of Propyl Gallate was reported to be 0.1% in other personal cleanliness products.

Some of these ingredients may result in incidental ingestion as they are used in lipstick and lip glosses (e.g., Propyl Gallate is used in lipsticks and lip glosses at up to 0.05%). Additionally, some of these ingredients are also used near the eye (e.g., Propyl Gallate is used in eyeliner at up to 0.02%) and in products that may result in exposure to mucous membranes (e.g., Propyl Gallate is used in bath soaps and body washes at up to 0.001%). Lastly, Propyl Gallate is reported to be used in baby products (i.e., baby lotions, oils, and creams at 0.00076%).

These ingredients may be used in sprays (e.g., Propyl Gallate is used in perfumes at 0.000023%) and powders (e.g., Propyl Gallate is used in face powders (concentration of use not stated)) and therefore may be incidentally inhaled. In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

It is possible that some products containing alkyl gallates may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined therein, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available, in some instances. None of the reported product categories for these ingredients as listed in the RLD include a designation using airbrush application, so it is possible that these ingredients are used with airbrush delivery systems, but not reported as such. Additionally, the concentration of use surveys are conducted based on product categories as stated in the RLD, but airbrush use was not reported in response to the survey. No consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with airbrush technology, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. If these ingredients were to be used in airbrush formulations, the data are insufficient to evaluate the exposure resulting from cosmetics applied in such a manner.

None of the alkyl gallates named in this report are restricted from use in any way under the rules governing cosmetic products in the European Union.[19]

Non-Cosmetic

Propyl Gallate is used as an antioxidant in foods to protect from rancidity.[2] *It is also used in essential oils and various food products (e.g., fats and oils, meats, candy, and beverages). According to 21CFR184.1660, Propyl Gallate is generally recognized as safe (GRAS) for use in food as an antioxidant. The FDA has placed the limit on the total antioxidant content (including Propyl Gallate) of food at 0.02% of the fat or oil content of the food (21CFR582.3660). Propyl Gallate may also be used in pressure-sensitive adhesives (21CFR175.125).*

Propyl Gallate is permitted for use as an antioxidant in food and food-contact applications including use in chewing gum base (21CFR172.615), as a component of resinous and polymeric coatings intending for food contact (21CFR175.300), and as an antioxidant that might migrate from food-packaging materials at levels not to exceed 0.005% (21CFR181.24). Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate are specifically permitted for use as an antioxidant/preservative in standardized margarine levels not to exceed 0.02% of the weight of the finished food (21CFR166.110). In addition to being used in foods and food products, Propyl Gallate is also used in FDA-approved drug products as an inactive ingredient (including oral and topical treatments; topical treatments have been reported to contain Propyl Gallate at 0.05%).[20]

TOXICOKINETIC STUDIES

Propyl Gallate

When Propyl Gallate (concentration not stated) was administered orally to rats, they primarily excreted 4-methoxygallic acid as the major urinary metabolite, with minor amounts of 2-methoxypyrogallol, gallic acid, and their glucuronides.[2] *Also in rats, after dietary exposure to Propyl Gallate (concentration not stated), the ester was largely unhydrolyzed in the gut and was excreted mostly unchanged in feces. In rabbits orally given Propyl Gallate (concentration not stated; method of oral administration not stated), much of the administered dose was eliminated in the urine, mainly as 4-*

methoxygallic acid glucuronide, with smaller amounts of pyrogallol and 4-methoxy gallic acid. Propyl Gallate (0.0117% in the diet) showed minimal absorption in dogs, with no detectable urinary excretion, after long-term dietary exposure.

Details regarding the dermal absorption, penetration enhancement, and absorption, distribution, metabolism, and excretion (ADME) studies summarized below may be found in Table 4.

Dermal absorption of Caprylyl Gallate (in water and ethanol; 1%) was evaluated in porcine skin, with approximately 14% percutaneous absorption (amount recovered in skin (epidermis and dermis) and receptor fluid) after a 24-h application.[21] In vitro intestinal permeability studies using Caco-2 (colorectal adenoma cell line) cell monolayers showed that Propyl Gallate (≤ 0.04 mg/ml) did not alter the permeability of model drugs (acyclovir, atenolol, ranitidine, or cimetidine).[22] An in vitro everted rat intestinal sac model evaluated Caprylyl, Dodecyl, and Propyl Gallate (100 mM), showing degrees of hydrolysis after 120 min of 1.01%, 0.012%, and 0.085%, respectively.[23] A physiologically-based kinetic (PBK) model of Caprylyl, Dodecyl, and Propyl Gallate predicted peak plasma concentrations (C_{max}) ranging from 18 ng/ml to 2089 ng/ml with apparent intrinsic clearance ($CLint_{app}$) values of 88 – 3662 µl/min/mg of S9 protein in rats and 88–3119 µl/min/mg of S9 protein in humans.[24] Following oral administration in rats, Caprylyl Gallate (25% in polyethylene glycol; 1000 µM/kg) and Dodecyl Gallate (25% polyethylene glycol in water; 1000 µM/kg) resulted in half-lives of 7.11 ± 1.78 h and 1.76 ± 0.79 h, respectively, as evaluated in plasma.[25] Radiolabeled Caprylyl Gallate (in polysorbate 80 and saline; 15 mg/kg) showed limited systemic absorption, with 60 – 80% of the administered dose remaining in the gastrointestinal tract up to 12 h post-dose (test substance administered via gavage).[26]

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Propyl Gallate

An acute dermal toxicity assay was performed according to Organisation for Economic Cooperation and Development (OECD) test guidelines (TG) 402.[4] Propyl Gallate (2000 mg/kg bw; moistened with water; 99.93% purity) was applied to the skin of Wistar rats (5/sex/dose) under semi-occlusive conditions (24-h application). No signs of irritation or mortality were observed. The LD_{50} was determined to be > 2000 mg/kg bw.

Oral

Propyl Gallate

Administration of Propyl Gallate resulted in oral median lethal dose (LD_{50}) values of 1.70 – 3.50 g/kg in mice, 2.1 – 7.0 g/kg in rats, 2.48 g/kg in hamsters, and 2.75 g/kg in rabbits.[2] Acute oral toxicity studies of cosmetic formulations containing ≤ 1% Propyl Gallate caused no deaths and minimal effects. Intraperitoneal administration in rats resulted in an LD_{50} of 0.38 g/kg with deaths occurring within 10 – 60 min due to cardiovascular or respiratory failure.

The acute oral toxicity of Propyl Gallate (125, 250, 500, 1000, or 2000 mg/kg bw; 20% hydroethanolic vehicle; > 99% purity) was evaluated in Fischer 344 rats (5/sex/dose) via gavage (assay performed to OECD TG 401).[4] The LD_{50} was determined to be > 2000 mg/kg bw.

Repeated-Dose Toxicity Studies

Propyl Gallate

Dermal toxicity was studied using 20% Propyl Gallate in lanolin (applied daily for 6 wk to the ears of guinea pigs; biopsies performed throughout test period and for 2 wk after discontinuation).[2] *Treatment resulted in reversible hyperplasia of the epidermis.*

Rats given up to 500 mg/kg/d Propyl Gallate via gavage for 1 wk showed slight, reversible fatty liver changes and abnormal mitotic figures in hepatocytes at ≥ 100 mg/kg/d.[2] *Mice and rats fed Propyl Gallate via diet for 14 d experienced mortality and reduced weight gain at high doses (≥ 50,000 ppm). No toxic effects were observed in rats given diets containing 0.5% Propyl Gallate for 6 wk. Similarly, Propyl Gallate (dose not stated) fed to rats for 1 or 3 mo 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. Mice and rats fed 170 – 520 mg/kg Propyl Gallate for 2.5 mo in the diet had reduced growth, decreased catalase, peroxidase, and cholinesterase activities. Mice and rats fed 170 – 520 mg/kg Propyl Gallate for 2.5 mo displayed reduced growth and decreased catalase, peroxidase, and cholinesterase activities. Rats fed 0.035 – 0.5% and pigs fed 0.2% Propyl Gallate in the diet for 3 mo showed no treatment-related effects on clinical, biochemical, or histopathological parameters. In a 13-wk study, rats fed ≤ 25,000 ppm Propyl Gallate via diet showed reduced weight gain, dirty tails, reddened duodenum, thickened stomach walls, and occasional gastric necrosis or inflammation. No significant effects in body weight, hematological parameters, organ weights, or mortality were observed in a 1-yr assay in which rats were fed a diet containing up to 20.25 mg Propyl Gallate/kg diet. Studies of 14 – 15 mo treatment in guinea pigs and dogs given 0.0117% Propyl Gallate in the diet showed no adverse effects on growth or organ health. Similarly, no significant toxic effects were observed when mice were given up to 1% Propyl Gallate in the diet for 90 wk. Reduced growth rates, anemia, kidney lesions, and mortality were observed in rats given 1.17 and 2.34% Propyl Gallate in the diet for 2 yr. No other*

pathological findings other than patchy hyperplasia in the stomach were observed in an assay in which rats were fed diets containing 5% Propyl Gallate for 2 yr.

Details on the repeated-dose toxicity studies summarized below may be found in Table 5.

In dietary studies, Caprylyl Gallate administered to rats at 0.5% for 12 d or 1% for 14 d had no effect on liver weight, with values comparable to untreated controls.[27,28] Similarly, Propyl Gallate at 1% in the diet for 14 d produced no changes in liver weight, while Dodecyl Gallate at 1% for 14 d caused a statistically significant increase in liver weight, compared to controls. In longer-term studies, Propyl Gallate (up to 12,500 ppm) was well-tolerated in a 13-wk dose-finding study in mice, with no effects on survival or microscopic pathology (test substance administered via diet).[4] In a 90-d study in rats, systemic effects (e.g., reduced body weight gain, decreased adrenal weight) were observed at the highest dose tested (7455 mg/kg feed); the no-observed-adverse-effect-level (NOAEL) was established at 1910 mg/kg feed (135 mg/kg bw/d).

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Propyl Gallate

No signs of fetal toxicity were observed following subcutaneous injection of 634 mg/kg Propyl Gallate (in water and ethanol) to pregnant rabbits on gestation day (GD) 12.[2] *No significant changes in growth or reproduction were observed in a multigenerational assay in which rats were treated via diet with up to 0.5% (450 mg/kg bw/d) Propyl Gallate). Similarly, pigs given 0.2% Propyl Gallate in the diet for more than 3 mo until a few litters had been produced displayed no significant abnormalities relating to growth or reproduction. A 2-generation study was performed in male and female rats given 1 – 10 mg/kg Propyl Gallate in butylhydroxyanisole via diet (details regarding treatment timing not stated). Rats given the test substance were unable to reproduce (control animals had offspring). Propyl Gallate (500 mg) given to female rats (from mating to GD 22) resulted in an increased fetal resorption rate (18.3% resorption) compared to controls (10.6% resorption). Pregnant rats fed diets containing up to 2.5% Propyl Gallate (GD 1 – 20) showed reduced maternal body weight and feed consumption at the highest dose, but no treatment-related fetal mortality or structural malformations, aside from a higher incidence of fetuses with fewer caudal vertebrae in the 2.5% group. Postnatally, decreased offspring viability in the 1 and 2.5% groups was attributed to maternal cannibalism rather than developmental toxicity. Across multiple species (rats, mice, and hamsters), Propyl Gallate given orally at doses up to 250 – 300 mg/kg produced no maternal or fetal toxicity (treatment on GD 6 – 10 to hamster and 6 – 15 to mice and rats. Similarly, maternal and fetal toxicity were not observed following oral administration of 2.5 – 250 mg/kg Propyl Gallate to rabbits on GD 6 – 18 or in guinea pigs treated with 0.0117% Propyl Gallate in the diet for 14 – 15 mo.*

Details regarding the developmental and reproductive toxicity studies summarized below may be found in Table 6.

In mouse oocytes, treatment with 150 – 250 µM Propyl Gallate in dimethyl sulfoxide (DMSO) reduced first polar body extrusion (PBE) and caused spindle, deoxyribonucleic acid (DNA), and mitochondrial damage, with complete oocyte degermation at 250 µM.[29] In 2-cell stage mouse embryos treated with Propyl Gallate (in potassium-modified simplex optimized medium and DMSO), exposure to 25 - 75 µM Propyl Gallate reduced progression to the 2- and 4-cell stages and induced oxidative stress, apoptosis, mitochondrial and lysosomal dysfunction, and altered epigenetic modifications at 50 µM.[30] Propyl Gallate (in DMSO; 50 mg/kg) resulted in dysregulated messenger ribonucleic acid (mRNA) expression of genes associated with various functions in the testis when given to mice via intraperitoneal injection for 4 wk.[31] Zebrafish embryos injected with 1 – 50 ppm Propyl Gallate (vehicle not stated) displayed dose-dependent, statistically significant malformations, altered hatching, and increased reactive oxygen species and apoptosis.[32]

GENOTOXICITY STUDIES

Propyl Gallate

In gene mutation assays, Propyl Gallate was non-mutagenic in Ames tests using Salmonella typhimurium at concentrations up to 1000 µg/plate with and without metabolic activation, although it was mutagenic in a rec-assay in Bacillus subtilis (concentration not stated).[2] *In chromosomal aberration assays, Propyl Gallate did not induce chromosomal aberrations or sister chromatid exchanges (SCEs) in diploid human embryo fibroblast cells at 0.0021 mg/ml, but chromosomal aberrations were observed in Chinese hamster fibroblast cells at 0.023 mg/ml (use of metabolic activation not stated) and in Chinese hamster ovary (CHO) cells at 0.25 – 1.5 mM (with metabolic activation). Propyl Gallate was tested for mutagenicity using host-mediated, cytogenetic, and dominant lethal assays, including both in vitro (up to 100 µg/ml in microbes and 50 µg/ml in human lung cells) and in vivo (up to 5000 mg/kg in mice and rats) studies. No significant increases in mutations, chromosomal aberrations, or dominant lethal effects were observed. Propyl Gallate (concentration not stated) was not mutagenic in an in vivo chromosomal aberration assay (in rat bone marrow) or a silkworm mutation assay.*

Details regarding the genotoxicity studies summarized below may be found in Table 7. In in vitro gene mutation assays, Propyl Gallate was non-mutagenic in Ames tests conducted with and without metabolic activation at concentrations up to 1000 µg/plate; however, it was mutagenic in a mouse lymphoma cell forward mutation assay performed without

metabolic activation at concentrations as low as 0.5 µg/ml.[33-35] In chromosomal damage assays, Caprylyl Gallate induced increases in SCEs in human lymphocytes at ≥ 0.063 µg/ml, but was non-clastogenic in a chromosomal aberration and micronucleus-based assays at concentrations ≤ 0.5 µg/ml (all assays performed without metabolic activation).[36] Propyl Gallate produced positive results in multiple mammalian cell systems including increased sister chromatid exchanges in CHO cells at ≥ 5 µg/ml without metabolic activation (≥ 50 µg/ml with metabolic activation), chromosomal aberrations at ≥ 40 µg/ml in Chinese hamster lung fibroblasts without metabolic activation, chromosomal aberrations at ≥ 5 µg/ml in CHO cells without metabolic activation (but not with metabolic activation up to 500 µg/ml), and micronucleus induction in several cell lines at concentrations generally ≥ 4.2 – 48 µg/ml without metabolic activation; results were negative in human lymphocytes at concentrations up to 225 µg/ml without metabolic activation, and equivocal in human liver cell line (HepG2) cells at 1485 µg/ml without metabolic activation.[33,37,38] In studies evaluating DNA strand breaks, Caprylyl Gallate was non-genotoxic in an alkaline comet assay at concentrations ≤ 0.5 µg/ml, but produced positive results at concentrations ≥ 100 µM (studies performed without metabolic activation).[33,37-39] Propyl Gallate was non-genotoxic in alkaline elution and modified comet assays at up to 500 µM, but induced DNA damage in an alkaline comet assay at 1000 µM in A549 human lung cancer cells (assays performed without metabolic activation).[4,33,37-41]

In vivo, Propyl Gallate was non-mutagenic in a mouse bone marrow micronucleus assay following intraperitoneal administration at doses up to 300 mg/kg bw/d and did not increase micronucleus frequency in an erythrocyte micronucleus test in mice intraperitoneally injected with 217 mg/kg bw/d Propyl Gallate.[42,43] Additionally, no DNA damage was observed in alkaline comet assays in rats and mice at oral doses up to 2000 mg/kg bw/d Propyl Gallate.[44]

CARCINOGENICITY STUDIES

Propyl Gallate

Propyl Gallate was tested for carcinogenicity in long-term dietary studies in mice (50/sex/group) and rats (50/sex/group), with doses of 6000 or 12,000 ppm fed for 103 wk.[2] *Propyl Gallate was not considered to be carcinogenic in mice (a significant increase in malignant lymphomas relative to concurrent controls were observed in high-dose male mice; but was not statistically-significant when compared to historical rate). Similarly, Propyl Gallate was not considered to be carcinogenic in 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 2 low-dose females (these effects were not considered related to the test substance). No significant differences were observed in the number of pulmonary tumors between test and control animals when Propyl Gallate was intraperitoneally injected in mice at doses of up to 2.4 g/kg, 3x/wk, for 8 wk.*

ANTI-CARCINOGENICITY STUDIES

Propyl Gallate

Propyl Gallate (0.01 – 0.75%) demonstrated selective antitumor activity in vitro by inhibiting key oxidation-reduction enzymes and reducing ribonucleic acid (RNA) content in tumor cells (type of tumor cell evaluated not stated).[2] *Propyl Gallate also suppressed mitosis in HeLa tumor cells (at 0.15 mg/ml) and inhibited RNA formation in Ehrlich ascites carcinoma cell preparations (at 10 – 40 µg/ml). In vivo, topically applied Propyl Gallate (50 µmol) to mouse skin inhibited 12-O-tetradecanoyl phorbol-13-acetate-induced ornithine decarboxylase activity, and Propyl Gallate (0.3%) fed to rats reduced dimethylbenzanthracene (DMBA)-induced tumor formation.*

Caprylyl Gallate

The effect of oral treatment (method of oral administration not stated) of Caprylyl Gallate (20 mg/kg bw; in DMSO; 14-wk treatment) on DMBA-induced breast cancer was evaluated in female Sprague-Dawley rats (6/group).[45] The induction and treatment period lasted for 3 mo. A positive control group consisting of animals induced with DMBA with no Caprylyl Gallate treatment was used for comparison. Serum tumor markers (carcinoembryonic antigen (CEA), cancer antigen 15.3 (CA 15.3) evaluated, and histopathological analyses of mammary tissues were performed after the treatment period. When compared to breast-cancer induced animals with no Caprylyl Gallate treatment, the oral administration of Caprylyl Gallate reduced the expression levels of CEA and CA 15.3 in a statistically significant manner. In addition, tissues from animals induced with breast cancer alone exhibited noticeable altered morphological structure compared to normal breast tissue. The cellular morphology of breast cancer tissues administered with Caprylyl Gallate showed almost normal tissue structure with minor or no remarkable changes.

Dodecyl Gallate

The effect of Dodecyl Gallate on DMBA-induced skin tumors was evaluated in IRC mice (4/sex/group).[46] In the established tumor arm, mice were first treated with DMBA to induce tumor formation, followed by a promotion phase consisting of topical application of 5 µg phorbol-12-myristate-13-acetate (PMA) until tumors developed. After measurable tumors appeared, Dodecyl Gallate (100, 250, or 500 µg) was applied topically 3x/wk for 8 wk. In the prevention arm, Dodecyl Gallate (2.5, 10, or 50 µg) was applied topically 3x/wk for 6 – 7 wk, beginning 15 d after DMBA initiation, during

the PMA promotion phase (5 µg), to assess inhibition of tumor formation. Tumor incidence and regression were evaluated at the end of the respective treatment periods. Regression of established tumors and prevention of tumor formation increased in a dose-dependent manner. Mean response rates were approximately 50% at intermediate dose levels for both prevention and regression.

OTHER RELEVANT STUDIES

Cellular Effects

Propyl Gallate

In vitro, Propyl Gallate stimulated human diploid fibroblast growth at 1 x 10^{-8} M, but inhibited proliferation at concentrations of 1 x 10^{-6} M or higher.[2] *Propyl Gallate also suppressed antibody production in mouse splenic cells at 5 µg/ml and reduced human and mouse cell multiplication at 20 µg/ml.*

Pulmonary Metabolism

Propyl Gallate

The effect of Propyl Gallate on mouse lung metabolism was evaluated in mice given a single intraperitoneal injection of up to 200 mg/kg Propyl Gallate. No significant pulmonary abnormalities or biochemical changes were observed.

Effects on Pigmentation

Propyl Gallate

The effect of Propyl Gallate on skin depigmentation was evaluated in black guinea pigs (n = 2- 5 animals/group).[2] *The test material (0.1 – 10% Propyl Gallate) was applied to the skin daily for 1 – 6 mo. Depigmentation was assessed regularly. Propyl Gallate did not result in depigmentation.*

Coagulant Effects

Propyl Gallate

In a swine femoral artery model, fibrin bandages supplemented with a platelet-activating reagent containing Propyl Gallate (amount of Propyl Gallate in reagent not stated) produced stronger clotting than control bandages that did not contain the reagent.[2] *Treated animals showed shorter bleeding times and higher residual platelet counts.*

Mutagenesis Enhancement

Propyl Gallate

Propyl Gallate (0.1 – 10 mM) enhanced the mutagenic effect of N-hydroxy-1-acetylaminofluorine and 4-nitroquinoline-1-oxide (4-NQO) in S. typhimurium strains TA98 and TA100, producing a 580 – 700% increase in mutation frequency without metabolic activation (effect not seen with metabolic activation).[2] *Propyl Gallate also induced a 700% increase in the mutagenic frequency of 4-NQO in TA98.*

Copper-Dependent DNA Damage

Propyl Gallate

Propyl Gallate at > 0.025 mM caused single-strand breaks with 5 µM copper(II)chloride and double-strand breaks with 100 µM copper(II)chloride when evaluated in the DNA of the Pseudomonas phage PM2.[2] *In human fibroblasts, 0.15 – 0.5 mM Propyl Gallate with 2.5 mM copper(II)chloride induced DNA strand breaks, whereas neither compound alone was damaging.*

Anti-Mutagenic Activity

Propyl Gallate showed antimutagenic activity in several in vitro assays, inhibiting dimethylnitrosamine-induced DNA damage, suppressing benzo[a]pyrene metabolite mutagenicity at 25 – 125 µM and 0.41 µmol/plate, and reducing mutagen formation from sugar-ammonia systems, albumin pyrolysis products, and several direct-acting mutagens.[2] *Propyl Gallate also decreased aflatoxin B_1 mutagenicity in S. typhimurium TA98 under metabolic activation; however, Propyl Gallate increased aflatoxin B_1 mutagenicity by 50 – 100% in TA100 at the highest dose tested (dose not stated).*

Neurological and Neuromuscular Effects

Propyl Gallate

Propyl Gallate (0.0001 M) was a strong, partially competitive inhibitor of bradykinin when evaluated in isolated guinea pig ileum.[2] *Propyl Gallate (1%) demonstrated local anesthetic activity comparable to procaine in rabbits and guinea pigs following intradermal injection, with effects enhanced by epinephrine. In mice, Propyl Gallate inhibited arachidonic acid-induced abdominal contractions when given intraperitoneally when mixed with arachidonic acid (2 mg/ml), as pretreatment (4 mg/kg), or simultaneously with arachidonic acid (100 µg/ml). Oral and subcutaneous administration of 10 or 40 mg/kg Propyl Gallate had no effect on arachidonic acid-induced contractions.*

Chemoprotection

Propyl Gallate

Propyl Gallate protected rats and mice against chemical-induced toxicity by acting as a free-radical scavenger and inhibiting lipid peroxidation.[2] *In rats, 30 – 300 mg/kg Propyl Gallate (route of administration not stated) reduced hepatotoxic and oxidative effects, and in mice, 0.75% dietary Propyl Gallate increased survival after 8 ppm phosgene exposure, while 1.5% Propyl Gallate showed no protective effects.*

Cytotoxicity

Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate

Multiple studies have evaluated the cytotoxic potential of alkyl gallates in a variety of in vitro cell models; representative findings from these studies are summarized herein. Caprylyl Gallate and Dodecyl Gallate were shown to be cytotoxic to murine melanoma (B16F10) cells at concentrations as low as 5 µM.[47] Dodecyl Gallate was also cytotoxic to human osteosarcoma (MG-63) cells at 6.25 µM and to human glioblastoma (U87) cells at 0.05 µM.[48,49] Caprylyl Gallate and Dodecyl Gallate were cytotoxic to rat hepatocytes at 1 mM, while Propyl Gallate demonstrated cytotoxicity in rat hepatocytes at concentrations as low as 0.5 mM.[50] Dodecyl Gallate exhibited cytotoxic effects against multiple human breast cancer cell lines at 0.5 µM, and Caprylyl Gallate was cytotoxic to pancreatic ductal adenocarcinoma cells at 10.3 µM.[51,52] Propyl Gallate was additionally cytotoxic to hepatocellular carcinoma cell lines at 10 µg/ml, lung cancer cells (Calu-6, A549) at 50 µM, and human pulmonary fibroblasts at 100 µM.[53-55] Propyl Gallate decreased mouse Leydig cell viability to below 50% at a 50 µM dose, while Sertoli cell viability was reduced by up to 44% following treatment with 10 µM, both effects being statistically significant compared to controls.[31]

Radiation/Photo Co-Effects

Propyl Gallate

Propyl Gallate demonstrated radioprotective and photoprotective activity in multiple in vivo and in vitro systems.[2] *In vivo, Propyl Gallate reduced radiation-induced tissue damage in mice and rats when administered orally at 0.25 – 0.5% in the diet or intraperitoneally at 30 – 150 mg/kg in mice and at 50 mg/kg in rats prior to sublethal irradiation. In vitro, Propyl Gallate inhibited DNA depolymerization, lipid peroxidation in lysosomal membranes, and gamma-radiation-induced mutagenicity (0.3 – 1 mg/ml). Propyl Gallate also resulted in photoprotective effects against ultraviolet light when topically applied to rats at 3 – 15 mg/animal in rats or up to 10% in guinea pigs.*

Propyl Gallate (concentration not stated) acted as a radiosensitizer in vivo, where repeated intraperitoneal injections of Propyl Gallate enhanced the tumor-killing effects of ionizing radiation in mice with lymphosarcomas.[2] *In contrast, in isolated DNA studies, Propyl Gallate showed radioprotective effects at concentrations up to 0.0165 M, however, prolonged pre-irradiation exposure reduced this protection, and in some cases, results in radio-sensitization.*

Inhibition of Nitrosamine Formation

Propyl Gallate (100 µmol/kg) inhibited nitrosamine formation from aminopyrine and sodium nitrite in rat stomachs by up to 55%.[2] *Likewise, in human saliva, Propyl Gallate (10 mM) reduced nitrosamine formation from the interaction of salivary nitrite with aminopyrine and oxytetracycline by 42 – 53%.*

Effect on Hepatotoxicity

Caprylyl Gallate and Propyl Gallate

In vitro, Propyl Gallate at 0.5 – 2.0 mM it caused dose-dependent rat hepatocyte toxicity.[2] *Oral administration of Propyl Gallate (dose not stated) also reduced trinitrotoluene-induced liver pathology in mice. In addition, intraperitoneal administration of 50 mg/kg Propyl Gallate with Caprylyl Gallate had a protective effect in rat liver tissue. Propyl Gallate prevented carbon tetrachloride-induced hepatic steatosis when administered at 200 mg/kg (route of administration not stated) to rats.*[2]

Anti-Microbial Activity

Propyl Gallate

Propyl Gallate shows broad antibacterial activity, though its effectiveness varies by organism and concentration.[2] *It can also act synergistically with other antimicrobials, enhancing the activity of antibiotics, and potentiating antifungal agents.*

Effect on Enzymes

Propyl Gallate

Propyl Gallate inhibits several redox and microsomal enzymes in vitro, including d-glyceraldehyde-3-phosphate dehydrogenase, lactic dehydrogenase, alcohol dehydrogenase, tyrosine hydroxylase (1–100 µM), aminopyrine demethylase, benzo[a]pyrene hydroxylase, azoreductases, and glucose-6-phosphatase, primarily via sulfhydryl oxidation and free-radical interference.[2] *In vivo studies in rats and guinea pigs (doses up to 0.3% in diet or 150 – 400 mg/kg/day intraperitoneally)*

showed minimal effects on cytochrome P450, aniline hydroxylase, amino pyrine N-demethylase, or microsomal protein, although hepatic uridine diphosphate-glucuronyltransferase activity was increased.

Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate

The inhibitory effects of Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate (tested in DMSO) on hyaluronidase and collagenase were evaluated in vitro.[56] Caprylyl Gallate had half-maximal inhibitory concentration (IC_{50}) values of 106 µM for hyaluronidase and 1.08 mM for collagenase, whereas Dodecyl Gallate and Propyl Gallate showed IC_{50} values > 1000 µM for hyaluronidase and >10 mM for collagenase. In 14-d dietary studies in male Sprague-Dawley rats (5/group), Caprylyl Gallate (1%) had no effect on hepatic enzymes, Dodecyl Gallate (1%) decreased benzo[a]pyrene-hydroxylase activity, and Propyl Gallate increased epoxide hydratase activity (effects evaluated compared to untreated controls).[28]

Inhibition of Developmental and Reproductive Toxicity

The effect of Propyl Gallate (0 – 0.4%) administration with and without vitamin E (via diet; length of test substance administration not stated) on teratogenicity inhibition was evaluated in vitamin E-deficient pregnant rats (rats killed on day 21 of gestation, and fetuses evaluated).[2] At 0.4% alone or at lower concentrations with vitamin E supplements, Propyl Gallate reduced teratogenic effects. The effect of Propyl Gallate (362 – 906 mg/kg; via injection) on hydroxyurea-induced teratogenesis was evaluated in rabbits. Propyl Gallate given simultaneously or as a mixed solution with hydroxyurea on GD 12 reduced the number and severity of malformations and resorptions; however, the highest dose was maternally toxic.

Renal Toxicity

Propyl Gallate

Propyl Gallate was evaluated in two 4-wk investigative studies in which female Beagle dogs (3/group) were given enteric-coated tablets containing Propyl Gallate at a target dose of 200 mg/kg/d (1 tablet/d; gavage administration).[57] Renal toxicity, characterized by tubular degermation and regeneration, increased urinary neutrophil gelatinase-associated lipocalin, and produced occasional increases in serum creatinine and urea nitrogen. In contrast, dogs that received tablets without Propyl Gallate or tablets containing other excipients did not exhibit these findings. In a follow-up study, administration of Propyl Gallate alone, at the same dose, in non-enteric gelatin capsules for 26 d did not result in renal toxicity.

Estrogenic Effects

Propyl Gallate

Propyl Gallate has been evaluated for estrogen and anti-estrogenic activity in multiple in vitro systems. The binding affinity (K_i) of Propyl Gallate (vehicle not stated) to estrogen receptor (ER)α was measured in MCF-7 breast cancer cells using a competition assay with 17β-estradiol, yielding a K_i of 0.054 µM for Propyl Gallate compared to 0.00003 µM for estradiol.[58] In an ERα-dependent luciferase reporter transactivation assay in MCF-7 cells, Propyl Gallate did not induce transcriptional activity, indicating that it functions as a pure ERα antagonist. When co-administered with 17β-estradiol, Propyl Gallate antagonized estradiol-induced transcription in a concentration-dependent manner, reducing activity by 33 and 40% at 0.01 and 0.1 µM, respectively.

The estrogenic potency of Propyl Gallate (in DMSO) was also assessed in an in vitro luciferase reporter assay using U2-OS cells (a human osteosarcoma cell line that lack endogenous ERs) transfected with ERα or ERβ.[59] Cells were exposed to Propyl Gallate (up to 50 µM) for 24 h, with estradiol and DMSO used as the positive and negative control, respectively. The lowest effect concentration (LEC), defined as the concentration producing an effect equal to the DMSO control plus three times the standard deviation, was 2.1 µM for ERα and 2.5 µM for ERβ, compared to 3×10^{-7} µM and 6.6×10^{-6} µM for estradiol, respectively.

In T47D-Kbluc breast cancer cells, Propyl Gallate (0.3–100 µM in DMSO) was evaluated in an estrogen-dependent reporter gene assay and in an estrogen-dependent proliferation assay in MCF-7 cells.[60] Dose-response curves showed that Propyl Gallate exhibited weak estrogenic activity in the luciferase assay but did not induce significant proliferation in MCF-7 cells. When co-administered with estradiol, Propyl Gallate demonstrated statistically significant anti-estrogenic activity in both assays.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Propyl Gallate

A suntan oil containing 0.003% Propyl Gallate was considered to be practically non-irritating when evaluated in rabbits in a modified Draize assay.[2] Similarly, a suntan cream containing 0.003% Propyl Gallate and a lipstick containing < 1% Propyl Gallate were not considered to be primary irritants when evaluated in primary skin irritation tests (assays performed using rabbits). No local lesions or primary irritation were observed when 10% Propyl Gallate in propylene glycol was applied to the skin of guinea pigs for 48 h.

In guinea pig maximization studies, Propyl Gallate at 0.1% (in alcohol) was non-sensitizing, while 0.5 – 2% induced sensitization (occlusive dermal challenge patches applied after intradermal induction period using 5% Propyl Gallate in adjuvant).[2] In a different assay, 10% Propyl Gallate in alcohol and olive oil was administered orally to guinea pigs daily for

7 d. After a 2-wk non-treatment period, animals were given intradermal injections of 5% Propyl Gallate and 0.05% dinitrochlorobenzene (DNCB), every other day, for 6 d. Additionally, 2 guinea pigs were given intradermal injections, but did not receive oral treatment with Propyl Gallate. Ten d after the final injection, 24-h occlusive challenge patches containing 0.1 – 2% Propyl Gallate or 0.01 – 0.1% DNCB. None of the Propyl Gallate-treated 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 to severe irritation to challenge patches containing 0.5 or 2% Propyl Gallate. A dermal sensitization assay was performed in which 20% Propyl Gallate in alcohol was routinely applied to guinea pig skin, under occlusion, over a 9-d induction period. Occlusive challenge patches containing 0.1 – 5% Propyl Gallate were applied 2 wk after the induction phase. Mild to moderate irritation was produced at concentrations of 1 and 5% Propyl Gallate during challenge, indicating sensitization. Sensitization was not observed at 0.1%. Propyl Gallate (5 – 25% in acetone and olive oil) was considered to be a sensitizer in a local lymph node assay (LLNA) performed in mice.

Cosmetic formulations containing < 1% Propyl Gallate were well-tolerated in human repeated-insult patch tests (HRIPT; n = 52 – 154) and cumulative irritancy tests (n = 12), with no significant irritation or sensitization observed in the majority of subjects.[2] *In contrast, positive reactions were observed in several patch tests (n = 1 – 10) using Propyl Gallate (0.01 – 1%; details regarding tests not provided). No dermal irritation was observed in a dermal irritation assay in which 10% Propyl Gallate in propylene glycol was evaluated in 2 subjects (24-h application). In an assay performed in 24 subjects, Propyl Gallate (20% in alcohol) was applied to the forearm 2x/wk for 24 d. During the last 10 d, 50% of subjects complained of pruritis and erythema, with 2 subjects developing skin eruptions. Investigators then applied a single 48-h patch containing 2% Propyl Gallate to 2 of the mildly sensitized reactors, and to 25 non-sensitive controls. Both sensitized subjects reacted mildly to the patch, whereas none of the control subjects reacted.*

Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate

A guinea pig sensitization assay was performed to study the sensitization potential of Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate.[2] *For induction, guinea pigs were injected with pure gallate mixed with saline and adjuvant over a 9-d induction period. After a non-treatment period, animals were challenged with applications of sub-irritant doses (specific doses not stated) of the gallates (occlusion not stated). Elicitation of cross-reactions was done on the opposite flank using the gallates at concentrations of 0.1 and 1%. All gallates tested were moderate to strong contact sensitizers, with Dodecyl Gallate being the strongest sensitizer. Sensitization potency increased with increasing alkyl chain length.*

Details regarding the dermal irritation and sensitization assays summarized below may be found in Table 8.

Propyl Gallate (applied neat; 10 ± 2 mg/tissue) was predicted to be a non-irritant in an in vitro reconstructed human epidermis model.[4] Propyl Gallate (up to 2%) showed expected predicted sensitization when used as a positive control in an in vitro reconstructed human epidermis-THP-1 coculture model developed for method evaluation.[61] Dodecyl Gallate (in DMSO; 1 – 50%) and Propyl Gallate (in acetone and olive oil; 5 – 25%) were sensitizing in LLNAs performed in mice.[62,63] Similarly, sensitization was observed in a guinea pig maximization test following treatment with Propyl Gallate (in saline; 0.35% (injection induction); 25% (dermal induction); 5% (dermal challenge)). In human studies in which patch tests were performed using Caprylyl Gallate (0.25%), Dodecyl Gallate (0.25%), and Propyl Gallate (1%) in 201 healthy subjects, the positivity rates were 0, 1.5, and 0%, respectively (vehicle was petroleum for all test substances).[64]

Phototoxicity/Photosensitization

The phototoxicity potential of a sun protection stick containing 0.003% Propyl Gallate was evaluated in guinea pigs.[2] *The product was applied to tape-stripped ears and irradiated for 2 h (appropriate controls used). The product was not considered to be phototoxic. No phototoxicity or photosensitization were observed in assays performed in subjects (n = 10 - 78) using cosmetic formulations (e.g., sunscreens) containing 0.003% Propyl Gallate. Similarly, no photosensitization was observed in an assay performed in 25 subjects using 10% Propyl Gallate in alcohol.*

OCULAR IRRITATION STUDIES

Propyl Gallate

A sun protection stick and a suntan cream containing 0.003% Propyl Gallate were considered to be non-ocular irritants when evaluated via Draize assays in rabbits.[2] *Six cosmetic formulations, each containing 0.003% Propyl Gallate, were evaluated in rabbits. None of these formulations were considered irritants. A lipstick formulation containing < 1% Propyl Gallate was also considered to be non-irritating in rabbit eyes (evaluated via Draize assay).*

In Vitro

Propyl Gallate

The eye irritation potential of Propyl Gallate (> 99.93% purity) was evaluated using a bovine corneal opacity and permeability assay according to OECD TG 437.[4] Propyl Gallate (20% suspension in saline; 750 µl) produced a mean in vitro irritation score (IVIS) of 29.65, while the negative control (vehicle) showed minimal effects (IVIS of 0.5) and the positive control (20% imidazole) induced marked corneal damage (mean IVIS 121.31). The IVIS obtained for the test substance did not allow for classification, as the score fell between the OECD cut-off values; therefore, no conclusion regarding eye

irritation or serious eye damage could be made from this assay. Because of this result, another study was subsequently conducted in rabbits; this study is summarized below.

Animal

Propyl Gallate

In an ocular irritation study performed according to OECD TG 405, a single ocular application of Propyl Gallate (0.1 g; 99.93% purity; applied neat) was administered to 1 eye of a male New Zealand White rabbit, and the untreated eye served as the control.[4] The treated eye was rinsed with saline 1 h post-application. Application resulted in severe, non-reversible ocular effects (including corneal opacity, iris lesions, conjunctival redness, and chemosis) over a 72-h observation period, resulting in classification as a severe eye irritant.

CLINICAL STUDIES

Retrospective and Prospective Studies

Numerous studies in the literature report patch testing with Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate, as these ingredients are included in expanded allergic patch test panels; many of these studies are summarized in Table 9. Patch testing studies indicate that Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate elicited positive reactions in up to 18%, up to 28%, and up to 12.5% of evaluated patients (of a variety of populations (e.g., allergic contact cheilitis, rosacea)), respectively.[65-79] Propyl Gallate generally showed lower sensitization rates, although a small but statistically-significant increase in positive reactions was noted over time (0.45% in 1988 - 1996 versus 0.77% in 1997 - 2005).

Occupational Exposure Study

Dodecyl Gallate

In an occupational clinical study, 10 workers exposed to washing powder containing 0.05% Dodecyl Gallate for 4 mo to 6 y underwent patch testing using occlusive silver patches, including standard series and washing powder components (Dodecyl Gallate 0.1% in olive oil).[80] Contact allergy was observed in 7/10 subjects, and 4/10 workers showed a type IV allergic reaction to Dodecyl Gallate. None of the 40 control subjects showed positive patch rest reactions to Dodecyl Gallate.

Consumer and Occupational Allergic Case Reports

Propyl Gallate

Case reports indicate that Propyl Gallate can cause allergic and irritant reactions in humans, primarily manifesting as contact dermatitis, cheilitis, or eczema.[2] *Numerous patch test studies and clinical reports demonstrate that topical exposure may elicit sensitization or dermatitis, with thresholds for positive reactions as low as 0.0025% in sensitive individuals. Cases span exposure via cosmetics, lotions, ointments, and occupational contact, with symptoms resolving upon discontinuation of the product.*

Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate

Patch tests were performed with various gallates including Caprylyl Gallate and Dodecyl Gallate (at 0.1 and 0.3%) in a Propyl Gallate-allergic individual.[2] *Positive reactions were observed at both concentrations for both Caprylyl and Dodecyl Gallate.*

Consumer and occupational case reports (Table 10) indicate that Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate can elicit allergic reactions in susceptible individuals.[73,81-92] Positive patch test responses were observed for Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate in cases of cheilitis, dermatitis, and facial or hand eruptions associated with cosmetics, personal care products, and occupational exposure, with symptoms resolving upon avoidance of the causative gallate.

Case Report – Depigmentation

Propyl Gallate

A 41-yr-old woman presented with depigmentation in the center forehead (corresponding to the bindi area) and the site of kumkum (a coloring usually made from turmeric or saffron for social/religious markings) application, which the patient had been using for 15 mo.[93] Bilaterally symmetrical depigmented lesions were also observed on the dorsal surfaces of both feet. The patient reported using lipstick, liquid kumkum in the hair parting and on the forehead, and strapped plastic or rubber slippers (gallates may be present in rubber footwear). Patch testing was performed using the Indian standard and cosmetic allergen series, as well as the patient's own kumkum and lipsticks (specific patch test details not provided). The site of Propyl Gallate application developed vesicles and ulcerations after 2 -3 d. The standard patch test was extended to 14 d, and the irregular depigmentation was seen at the Propyl Gallate application site, with negative results for all other allergens. The patient was advised to avoid using cosmetics containing Propyl Gallate and slippers made of plastic and rubber materials. (Partial re-pigmentation was observed after 6 mo of treatment with a topical steroid and tacrolimus.)

SUMMARY

The 4 alkyl gallates evaluated in this report are all reported to function in cosmetics as antioxidants. Propyl Gallate was first reviewed by the Panel in a safety assessment published in 1985, with the conclusion that Propyl Gallate is safe as a cosmetic ingredient at concentrations not exceeding 1%. In 2007, after the review of new data, a Final Amended Report was published with the conclusion that Propyl Gallate is safe in the present practices of use as described in that safety assessment at concentrations less than or equal to 0.1%. In June 2024, this ingredient was re-reviewed, and the report was re-opened for the evaluation of new data and for the addition of structurally similar ingredients.

According to RLD obtained from the FDA in 2025, Propyl Gallate is used in 1127 total formulations, at up to 0.1% (in leave-on face and neck products). All other ingredients are reported to be used in 21 formulations or less. No concentrations of use were reported for the remaining alkyl gallates. When determining whether to re-open the safety assessment on Propyl Gallate, the Panel considered that, according to 2023 VCRP data, Propyl Gallate was reported to be used in 86 formulations as opposed to 164 formulations reported in 2002. The reported maximum concentration of use has remained the same (in 2003, the maximum concentration of use of Propyl Gallate was reported to be 0.1%).

Dermal absorption of Caprylyl Gallate (1% in water and ethanol) in porcine skin was approximately 14% after a 24-h application. In Caco-2 cells, Propyl Gallate (≤ 0.04 mg/ml) did not alter the permeability of model drugs. An in vitro everted rat intestinal sac model evaluated Caprylyl, Dodecyl, and Propyl Gallate (100 mM), showing degrees of hydrolysis after 120 min of 1.01%, 0.012%, and 0.085%, respectively. PBK modeling of Caprylyl, Dodecyl, and Propyl Gallate predicted C_{max} values ranging from 18 to 2089 ng/ml. Oral administration in rats of Caprylyl Gallate and Dodecyl Gallate (1000 µM/kg) resulted in half-lives of 7.1 and 1.8 h, respectively. Radiolabeled Caprylyl Gallate (15 mg/kg; gavage) showed 60 – 80% of the dose remained in the gastrointestinal tract up to 12 h post-dose.

In an acute dermal toxicity study in rats, Propyl Gallate (2000 mg/kg bw) caused no mortality or irritation, with an LD_{50} greater than 2000 mg/kg bw. Similarly, in an acute oral toxicity study in rats, doses up to 2000 mg/kg bw produced no mortality, with an LD_{50} also exceeding 2000 mg/kg bw.

In short-term (12 to 14-d) dietary studies, Caprylyl Gallate (0.5 - 1%) and Propyl Gallate (1%) had no effect on liver weight, while Dodecyl Gallate (1%) caused a statistically significant increase compared to controls. In longer-term studies, Propyl Gallate (up to 12,500 ppm in the diet) was well-tolerated in mice for 13 wk, and a 90-d rat study established an NOAEL of 1910 mg/kg feed (135 mg/kg bw/d).

In vitro, Propyl Gallate reduced first polar body extrusion and caused spindle, DNA, and mitochondrial damage in mouse oocytes (150 – 250 µM) and impaired 2-cell stage embryo development, inducing oxidative stress, apoptosis, and mitochondrial and lysosomal dysfunction (25 – 75 µM). Zebrafish embryos exposed to 1 – 50 ppm exhibited dose-dependent malformations, delayed hatching, and increased oxidative stress and apoptosis. Propyl Gallate (50 mg/kg) resulted in dysregulated mRNA expression of genes associated with various functions in the testis when evaluated given to mice via intraperitoneal injection for 4 wk.

In vitro, Propyl Gallate was non-mutagenic in Ames assays (up to 1000 µg/plate, with and without metabolic activation) but was mutagenic in a mouse lymphoma cell assay without metabolic activation at concentrations as low as 0.5 µg/ml. Caprylyl Gallate increased SCEs in human lymphocytes at ≥ 0.063 µg/ml but was non-clastogenic in chromosomal aberration and micronucleus assays at ≤ 0.5 µg/ml. Propyl Gallate induced chromosomal damage and micronucleus formation in multiple mammalian cell lines at concentrations generally ≥ 4.2 – 48 µg/ml without metabolic activation, with equivocal results in HepG2 cells at 1485 µg/ml. In DNA strand break assays, Propyl Gallate was non-genotoxic in alkaline elution and modified comet assays up to 500 µM but produced DNA damage in A549 cells at 1000 µM, while Caprylyl Gallate was positive at ≥ 100 µM but negative at ≤ 0.5 µg/ml; all assays were conducted without metabolic activation. In vivo, Propyl Gallate was non-mutagenic in mouse bone marrow and erythrocyte micronucleus tests (doses up to 300 mg/kg bw/d and 217 mg/kg bw/d, respectively; intraperitoneal administration) and did not induce DNA damage in alkaline comet assays in rats and mice at oral doses up to 2000 mg/kg bw/d.

Oral administration of Caprylyl Gallate (20 mg/kg bw for 14 wk) in female rats reduced serum tumor markers (CEA and CA 15.3) and preserved near-normal mammary tissue morphology in a DMBA-induced breast cancer model. Topical application of Dodecyl Gallate (2.5 - 500 µg; 3x/wk; 6 – 8 wk) dose-dependently prevented tumor formation and promoted regression of established DMBA-induced skin tumors.

Alkyl gallates have demonstrated cytotoxicity in multiple in vitro cell models. Caprylyl and Dodecyl Gallate were cytotoxic to murine melanoma cells at 5 µM and to rat hepatocytes at 1 mM and Dodecyl Gallate was cytotoxic to human osteosarcoma cells at 6.25 µM and glioblastoma (U87) cells at 0.05 µM. Propyl Gallate showed cytotoxicity in rat hepatocytes at 0.5 mM, hepatocellular carcinoma cells at 10 µg/ml, lung cancer cells at 50 µM, and human pulmonary fibroblasts at 100 µM. Propyl Gallate significantly reduced mouse Leydig cell viability at 50 µM and Sertoli cell viability at 10 µM

The inhibitory effects of Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate on hyaluronidase and collagenase were evaluated in vitro. Caprylyl Gallate showed IC_{50} values of 106 µM for hyaluronidase and 1.08 mM for collagenase, while Dodecyl Gallate and Propyl Gallate had IC_{50} values > 1000 µM for hyaluronidase and > 10 mM for collagenase. In 14-d

dietary studies in rats, Caprylyl Gallate (1%) had no effect on hepatic enzymes, Dodecyl Gallate (1%) decreased benzo[a]pyrene-hydroxylase activity, and Propyl Gallate increased epoxide hydratase activity.

In two 4-wk studies, female Beagle dogs given enteric-coated tablets containing Propyl Gallate (200 mg/kg/d) exhibited renal toxicity, including tubular degeneration and regeneration, increased urinary neutrophil gelatinase-associated lipocalin, and occasional increases in serum creatinine and urea nitrogen. In a follow-up 26-d study, administration of Propyl Gallate alone in non-enteric gelatin capsules at the same dose did not produce renal toxicity.

Propyl Gallate has been evaluated for estrogenic and anti-estrogenic activity in multiple in vitro systems. Propyl Gallate bound to ERα with a K_i of 0.054 μM (vs. 0.00003 μM for estradiol) and acted as a pure ERα antagonist in a luciferase reporter assay, reducing estradiol-induced transcription by up to 40% at 0.1 μM. In additional reporter and proliferation assays, Propyl Gallate showed weak estrogenic activity but did not stimulate MCF-7 cell proliferation and exhibited statistically significant anti-estrogenic effects when co-administered with estradiol.

Propyl Gallate (10 ± 2 mg/tissue) was predicted to be a non-irritant in an in vitro reconstructed human epidermis model. Propyl Gallate (up to 2%) showed an expected response of predicted sensitization when used as a positive control in a reconstructed human epidermis-THP-1 coculture model developed for method evaluation. Dodecyl Gallate (1 - 50%) and Propyl Gallate (5 – 25%) were sensitizing in mouse LLNAs, and Propyl Gallate (0.35% injection induction; 25% dermal induction; 5% dermal challenge) also induced sensitization in a guinea pig maximization test. In human studies in which patch tests were performed using Caprylyl Gallate (0.25%), Dodecyl Gallate (0.25%), and Propyl Gallate (1%) in 201 healthy subjects, the positivity rates were 0, 1.5, and 0%, respectively

The eye irritation potential of Propyl Gallate was initially evaluated in a bovine corneal opacity and permeability assay where a 20% suspension produced a mean in vitro irritation score of 29.65, falling between OECD cut-offs and preventing definitive classification. In a follow-up study, a single ocular application of neat Propyl Gallate (0.1 g) to a rabbit caused severe, non-reversible effects, resulting in classification as a severe eye irritant.

Patch testing studies have evaluated Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate in a variety of populations, including patients with allergic contact cheilitis, rosacea, and dermatitis. Overall, Propyl Gallate showed lower sensitization rates compared to Dodecyl and Caprylyl Gallate. For Propyl Gallate specifically, a small but statistically-significant increase in positive reactions were observed over time (0.45% in 1988 – 1996 versus 0.77% in 1997 – 2005).

In an occupational clinical study, 10 workers were exposed to washing powder containing 0.05% Dodecyl Gallate. Four of the 10 workers (40%) had a type IV allergic reaction to Dodecyl Gallate (0.1% in olive oil) upon patch testing.

A 41-yr-old woman developed depigmented lesions on the forehead and dorsal feet after prolonged use of kumkum-containing cosmetics and plastic or rubber slippers. Patch testing identified Propyl Gallate as the causative allergen, producing vesicles and ulcerations at the application site, while all other allergens tested negative. The patient was advised to avoid Propyl Gallate-containing products, and partial re-pigmentation was observed after 6 mo of treatment with topical steroid and tacrolimus.

Consumer and occupational case reports demonstrate that Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate can cause allergic reactions in susceptible individuals. Positive patch test responses were reported for all three ingredients in cases of cheilitis, dermatitis, and facial or hand eruptions related to cosmetics, personal care products, or occupational exposure, with symptoms generally resolving after avoidance of the offending gallate.

DISCUSSION

In accordance with its Procedures, the Panel re-evaluates the conclusions of previously-issued reports approximately every 15 years. In 1985, the Panel published a final report on Propyl Gallate and concluded that this ingredient was safe as a cosmetic ingredient at concentrations not exceeding 1%. In 2007, after reviewing new data indicating positive patch test results at 0.5% Propyl Gallate, a Final Amended Report was published with the conclusion that Propyl Gallate is safe in the present practices of use as described in that safety assessment at concentrations less than or equal to 0.1%. As it had been at least 15 years since the Amended Report was published, the Panel reconsidered the safety of Propyl Gallate in June 2024, and determined to re-open this safety assessment due to new toxicity data, and for the inclusion of other in-use alkyl gallates that had not been reviewed by the Panel (i.e., Caprylyl Gallate, Dodecyl Gallate, and Ethylhexyl Gallate). After evaluation of previous and new data (including 2025 RLD), and in accordance with the product categories and concentrations of use identified in the Use section and Use table, the Panel issued a conclusion stating that these 4 alkyl gallates are safe in cosmetics when formulated to be non-irritating and non-sensitizing.

Safety for this group was supported by the fact that most of these ingredients are approved by the US FDA for use as antioxidants/preservatives in food. Additionally, Propyl Gallate is used in approved oral and topical drug products. Further evidence of safety comes from a 2-yr carcinogenicity assay with Propyl Gallate, which yielded negative results. These results provide additional support for the overall safety of the ingredients.

The Panel also reviewed several in vitro studies reporting estrogenic activity for Propyl Gallate. However, these findings were not considered relevant to cosmetic use, given the doses and routes of exposure, and were further mitigated by results from a multigenerational assay showing no developmental or reproductive toxicity.

A case report describing skin depigmentation following use of products containing gallates was also considered. This effect was determined to represent post-inflammatory hypopigmentation resulting from the severity of the reaction, rather than a direct effect on melanogenesis.

Concern was expressed regarding heavy metals that may be present in this ingredient. It was emphasized that the cosmetics industry should continue to use appropriate procedures to minimize impurities in cosmetic formulations, in accordance with limits set by the US FDA and Environmental Protection Agency.

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (e.g., Propyl Gallate is used in perfumes at 0.000023% and in face powders (concentration of use not reported)). Inhalation toxicity data were not available. However, the Panel noted that the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern. Although frequency and concentration of use data are now available (and in some cases mandated) for ingredients marketed for use with airbrush delivery systems in certain product categories, no data are available for consumer habits and practices thereof, product particle size, or other relevant particle data (e.g., diameter). As a result of deficiencies in these critical data needs, the data profile is incomplete, and the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Accordingly, the Panel has concluded that if these ingredients are used in airbrush formulations, the data are insufficient to support safe use when applied with such delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 4 alkyl gallates are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating and non-sensitizing:

Caprylyl Gallate
Dodecyl Gallate
Ethylhexyl Gallate
Propyl Gallate

TABLES

Table 1. Definitions, idealized structures, and reported functions[3,CIR Staff]

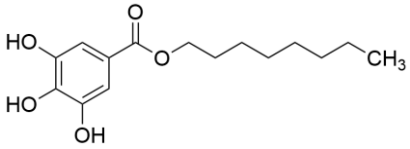
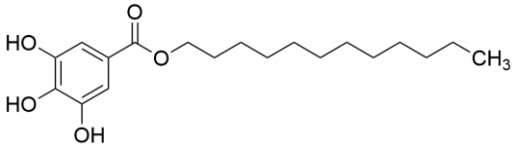
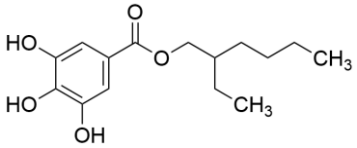
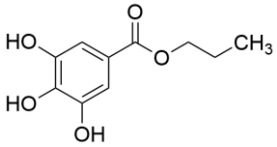
Ingredient/CAS No.	Definition	Function(s)
Caprylyl Gallate [CAS No. 1034-01-1]	Caprylyl Gallate is the organic compound that conforms to the structure: 	Antioxidant
Dodecyl Gallate [CAS No. 1166-52-5]	Dodecyl Gallate is the ester of gallic acid that conforms to the structure: 	Antioxidant
Ethylhexyl Gallate [CAS No. 34531-26-5]	Ethylhexyl Gallate is the ester of 2-ethylhexanol and gallic acid. It conforms to the structure: 	Antioxidant
Propyl Gallate [CAS No. 121-79-9]	Propyl Gallate is the aromatic ester of propyl alcohol and gallic acid. It conforms generally to the structure: 	Antioxidant; Fragrance Ingredient

Table 2. Chemical properties

Property	Value	Reference
Caprylyl Gallate		
Physical Form	solid	10
Color	white	10
Odor	odorless	10
Molecular Weight (g/mol)	282.3	10
Melting Point (ºC)	94 - 95	10
Water Solubility (g/l @ 20º C)	0.036	10
log K_{ow}	3.66	10
Disassociation Constant (pKa)	7.94	24
Dodecyl Gallate		
Physical Form	solid	9
Color	white	9
Odor	odorless	9
Molecular Weight (g/mol)	338.4	9
Melting Point (ºC)	96 - 97	9
Water Solubility	insoluble	9
Other Solubility (ethanol, ether)	freely soluble	9
log K_{ow}	6.75 (estimated)	11
Disassociation Constants (pKa)	7.93	24
Skin penetration coefficient (Kp; cm/h)	-2.51 (estimated)	62
Ethylhexyl Gallate		
Molecular Weight (g/mol)	282.33	8
Melting Point (ºC)	172.71	7
Boiling Point (ºC)	414.61	7
Vapor Pressure (mmHg @ 25º C)	5.02×10^{-9}	7
Water Solubility (g/l @ 25º C)	0.016	7
log K_{ow}	4.17 (estimated)	7
Propyl Gallate		
Physical Form	crystalline powder	2
Color	white to light brown	2
Odor	odorless	2
Molecular Weight (g/mol)	212.2	2
Specific Gravity	1.21	94
Vapor Density (mmHg)	7.3	94
Melting Point (ºC)	146 - 150	2
Water Solubility (g/l @ 25º C)	3.49	94
Other Solubility	soluble in ethanol, ethyl ether, oil, lard, aqueous solutions of polyethylene glycol ethers of cetyl alcohol*	2
log K_{ow}	1.80	2
Disassociation Constants (pKa)	8.11	2
UV Absorption** (λ) (nm) (alcohol)	275	2
UV Absorption (λ) (nm) (water)	217, 274	94
pH (0.05, 0.1, and 0.2% aqueous)	6.3, 5.9., 5.7	2

*Solubility increases as the concentrations of the surfactant increases and the polyethylene glycol chain length increases.
**Absorption shifts to higher wavelengths at higher concentrations; increasing Propyl Gallate concentration broadens curve to 290 – 320 nm. At 10%, the absorption peak is greater than 390 nm.

Table 3. Frequency and concentration of use according to likely duration and exposure and by product category[15-17]

	Caprylyl Gallate*		Dodecyl Gallate		Ethylhexyl Gallate		Propyl Gallate	
	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use
	RLD (2025)	% (2024)	RLD (2025)	% (2024)	RLD (2025)	% (2024)	RLD (2025)	% (2024)
Totals**	**1**	**NR**	**4**	**NR**	**21**	**NR**	**1127**	**0.0000024 – 0.1**
summarized by likely duration and exposure***								
Duration of Use								
Leave-On	*1*	*NR*	*4*	*NR*	*21*	*NR*	*1074*	*0.000003 – 0.1*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*66*	*0.0000024 – 0.0037*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*3*	*NR*
Unknown	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*33*	*NR*
Exposure Type								
Baby Products	NR	NR	NR	NR	NR	NR	NR	0.00076
Children's Makeup	NR	NR	NR	NR	NR	NR	NR	NR
Eye Area	NR	NR	NR	NR	8	NR	40	0.02
Incidental Ingestion	NR	NR	NR	NR	2	NR	747	0.0003 – 0.05
Mucous Membrane	NR	NR	NR	NR	2	NR	765	0.0000024 – 0.05
Incidental Inhalation-Spray	1[a]	NR	2[a]	NR	NR	NR	25; 189[a]; 55[b]	0.000023; 0.0037[b]
Incidental Inhalation-Airbrush	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	1[a]	NR	1; 2[a]	NR	5	NR	9; 189[a]	0.000003 – 0.1[c]
Dermal Contact	1	NR	4	NR	18	NR	361	0.0000024 – 0.1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	12	0.003
Hair-Coloring	NR	NR	NR	NR	NR	NR	2	NR
Nail	NR	NR	NR	NR	NR	NR	2	0.00026
Other Preparations (Unknown Exposure Type)	NR	NR	NR	NR	NR	NR	33	NR
as reported by product category								
Baby Products								
Baby Lotions/Oils/Powders/Creams							NR	0.00076
Bath Preparations (diluted for use)								
Bath Oils, Tablets, and Salts							3	NR
Eye Makeup Preparations (not children's)								
Eyebrow Pencil							3	NR
Eyeliner					2	NR	2	0.02
Eye Shadow					3	NR	4	NR
Eye Lotion							5	NR
Eye Makeup Remover							1	NR
Mascara					1	NR	19	NR
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)					2	NR	2	NR
Other Eye Makeup Preparations							4	0.02
Fragrance Preparations								
Cologne and Toilet Water							1	NR
Perfumes							23	0.000023
Hair Preparations (non-coloring)								
Hair Conditioners							4 (r.o.)	0.003 (r.o.)
Hair Sprays (aerosol fixatives)							1	NR
Shampoos (non-coloring)							3 (r.o.)	NR
Tonics, Dressings, Other Hair Grooming Aids							1	NR
Other Hair Preparations							2 (l.o.); 1 (r.o.)	NR

Table 3. Frequency and concentration of use according to likely duration and exposure and by product category[15-17]

	Caprylyl Gallate*		Dodecyl Gallate		Ethylhexyl Gallate		Propyl Gallate	
	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use
	RLD (2025)	% (2024)	RLD (2025)	% (2024)	RLD (2025)	% (2024)	RLD (2025)	% (2024)
Hair Coloring Preparations								
Hair Dyes and Colors (all types requiring caution statements and patch tests)							2	NR
Makeup Preparations (not eye or children's)								
Blushers and Rouges (all types)					3	NR	NR	0.045
Face Powders			1	NR	5	NR	9	NR
Foundations					2 (traditional application)	NR	11 (traditional application)	NR
Leg and Body Paints							5 (traditional application)	NR
Lipsticks and Lip Glosses					2	NR	747	0.0003 – 0.05
Makeup Bases					1 (traditional application)	NR		NR
Makeup Fixatives							1	NR
Other Makeup Preparations			1 (traditional application)	NR			9 (traditional application)	NR
Manicuring Preparations								
Nail Creams and Lotions							1	0.00026
Nail Polish and Enamel							1	
Oral Hygiene Products								
Mouthwashes and Breath Fresheners							NR	0.0037
Personal Cleanliness								
Bath Soaps and Body Washes							14	0.0000024 – 0.001
Other Personal Cleanliness Products							1 (r.o.)	NR
Skin Care Preparations								
Cleansing							16	NR
Face and Neck (excluding shaving preps)	1 (l.o.)	NR	2 (l.o.)	NR			158 (l.o.); 15 (r.o.)	0.000003 – 0.1 (l.o.; not spray)
Body and Hand (excluding shaving preps)							5 (l.o.)	0.00055 (l.o.; not spray)
Foot Powders and Sprays							1	NR
Moisturizing							22	0.00055 (not spray)
Night							11	NR
Skin Fresheners							4	NR
Other Skin Care Preparations							2 (r.o.)	NR
Other Preparations (i.e., those that do not fit another category)							33	NR

NR – not reported
l.o. – leave-on; r.o. – rinse-off
*Use reported under the trade name "octyl gallate"; no uses reported under INCI name
**The sum of the counts given for duration of use and by exposure type, and the sum of the frequency reported by product category, may not equal the sum of total uses because each ingredient may be used in cosmetic formulations that are reported under more than one product category.
***Likely duration and exposure are derived from survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)
[a] 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
[b] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 4. Toxicokinetics studies

Test Article	Vehicle	Test System	Dose/Concentration	Protocol	Results	Reference
DERMAL ABSORPTION						
Caprylyl Gallate	water and ethanol	porcine skin (6 samples)	10 µl; 1%	in vitro percutaneous absorption study; test substance applied to skin for 24 h; non-occlusive conditions; quantification of test substance in skin surface wash, stratum corneum, epidermis, dermis, receptor fluid (receptor fluid consisted of phosphate-buffered saline in distilled water)	distribution of test substance: surface excess: 52.28 ± 2.09% stratum corneum: 24.97 ± 1.89% epidermis: 6.36 ± 0.69% dermis: 6.15 ± 0.31% receptor fluid: 1.47 ± 0.25% total recovery: 91.33 ± 1.64% percutaneous absorption: 13.98 ± 0.51% (amount recovered in skin (epidermis and dermis) and receptor fluid)	[21]
PENETRATION ENHANCEMENT						
Propyl Gallate	NR	in vitro intestinal permeability model using Caco-2 cell monolayers (6 replicates/concentration)	0, 0.01, 0.02, 0.04 mg/ml	effect of Propyl Gallate on the permeability of acyclovir, atenolol, ranitidine, and cimetidine evaluated; unidirectional permeation assessment; test compounds applied to the apical side either alone or with Propyl Gallate; samples collected on basolateral side and quantified and P_{app} calculated	Propyl Gallate had no observable impact on the permeability of acyclovir, atenolol, ranitidine, or cimetidine mean P_{app} (cm/s) values: acyclovir: control = 0.000000425; with Propyl Gallate = 0.000000362 – 0.000000435 atenolol: control = 0.000000445; with Propyl Gallate = 0.000000364 – 0.000000445 ranitidine: control = 0.000000409; with Propyl Gallate = 0.000000348 – 0.000000405 cimetidine: control = 0.000000619; with Propyl Gallate = 0.000000605 – 0.000000727	[22]
ADME						
In Vitro						
Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate	methanol	everted rat small intestine sacs (Sprague-Dawley rats)	100 µl; 100 mM	excised small intestine fragments tied to form sacs and everted; mucosal side exposed; test substance added to mucosal solution (bicarbonate-buffered salt solution); sacs incubated 15 – 120 min; hydrolysis to gallic acid measured; gallic acid transport quantified	All alkyl gallates hydrolyzed to gallic acid, contributing to gallic acid transport. The hydrolysis rate of the alkyl gallates increased and then decreased with chain length, exhibiting a maximum for Caprylyl Gallate. Degree of hydrolysis after 120 min: Caprylyl Gallate = 1.0053%, Dodecyl Gallate = 0.0119%, Propyl Gallate = 0.0852%	[23]
In Silico						
Caprylyl Gallate	NA	generic human and rat PBK models (web-based QIVIVE toolbox)	oral dose model (17.5 mg/kg bw in rats)	intrinsic clearance measured in liver S9 fractions; physicochemical and kinetic parameters used for PBK modeling	C_{max} (17.5 mg/kg bw Caprylyl Gallate, rat); 29 ng/ml $CLint_{app}$ (rat): 3662 µl/min/mg of S9 protein $CLint_{app}$ (human): 3119 µl/min/mg of S9 protein	[24]
Dodecyl Gallate	NA	generic human and rat PBK models (web-based QIVIVE toolbox)	oral dose model (10 mg/kg bw in rats)	same as above	C_{max} (10 mg/kg bw Dodecyl Gallate, rat); 18 ng/ml $CLint_{app}$ (rat): 232 µl/min/mg of S9 protein $CLint_{app}$ (human): 88 µl/min/mg of S9 protein	[24]

Table 4. Toxicokinetics studies

Test Article	Vehicle	Test System	Dose/Concentration	Protocol	Results	Reference
Propyl Gallate	NA	generic human and rat PBK models (web-based QIVIVE toolbox)	oral doses model (14 and 135 mg/kg bw in rats; 1.4 and 14 mg/kg bw in humans)	same as above	C_{max} (14 mg/kg bw Propyl Gallate, rat); 217 ng/ml C_{max} (135 mg/kg bw Propyl Gallate, rat); 2089 ng/ml C_{max} (1.4 mg/kg bw Propyl Gallate, human); 27 ng/ml C_{max} (14 mg/kg bw Propyl Gallate, human); 274 ng/ml $CLint_{app}$ (rat): 818 µl/min/mg of S9 protein $CLint_{app}$ (human): 428 µ/min/mg of S9 protein	[24]
				Oral		
Caprylyl Gallate	25% polyethylene glycol in water	7 male Sprague-Dawley rats	1000 µM/kg	rats given single gavage dose; samples of blood obtained 0, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, and 24 h after administration; pharmacokinetic parameters evaluated (C_{max1}, C_{max2}, C_{max3}, T_{max1}, T_{max2}, T_{max3}, $T_{1/2}$)	C_{max1} = 22.38 ± 6.71 µM C_{max2} = 7.27 ± 4.57 µM C_{max3} = 4.76 ± 3.23 µM T_{max1} = 0.25 h T_{max2} = 2 h T_{max3} = 12 h $T_{1/2}$ = 7.11 ± 1.78 h	[25]
^{14}C-labelled Caprylyl Gallate	polysorbate 80 and saline	female Wistar rats (1/group)	15 mg/kg	rats given single oral dose (gavage); animals killed at 10 min, 30 min, 6 h, and 12 h after dosing; samples collected: carcass, gut wall/contents, urine, expired air	approximately 20 – 30% of the radioactivity administered was detected in the tissues following administration,; and 60 – 80% of the dose was found in the contents of the gastrointestinal tract up to 12 h after administration recovery of radioactivity after 10 min: carcass: 12.7% gut wall: 13.7% gut contents: 74% expired air: 0.4% urine: 0.1% feces: not detected recovery of radioactivity after 12 h: carcass: 6.4% gut wall: 2% gut contents: 61% expired air: 19.6% urine: 6% feces: not detected	[26]
Dodecyl Gallate	25% polyethylene glycol in water	7 male Sprague-Dawley rats	1000 µM/kg	rats given single gavage dose; samples of blood obtained 0, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, and 24 h after administration; pharmacokinetic parameters evaluated (C_{max1}, C_{max2}, C_{max3}, T_{max1}, T_{max2}, T_{max3}, $T_{1/2}$)	C_{max1} = 0.15 ± 0.03 µM C_{max2} = 0.16 ± 0.04 µM C_{max3} = 0.04 ± 0.02 µM T_{max1} = 0.25 h T_{max2} = 2 h T_{max3} = 12 h $T_{1/2}$ = 1.76 ± 0.79 h	[25]

C_{max} = peak plasma concentration; C_{max1} = first peak plasma concentration; C_{max2} = second peak plasma concentration; C_{max3} = third peak plasma concentration; Caco-2 = colorectal adenocarcinoma cells; $CLint_{app}$ = apparent intrinsic clearance; CMC = carboxymethylcellulose; DMSO = dimethyl sulfoxide; NA = not applicable; NR = not reported; P_{app} = apparent permeability coefficient; PBK = physiologically-based kinetic; $T_{1/2}$ = plasma half-life, T_{max} = time to reach peak plasma concentration; T_{max1} = time to reach C_{max1}; T_{max2} = time to reach C_{max2}; T_{max3} = time to reach C_{max3}; QVIVE = quantitative in vitro to in vivo extrapolation

Table 5. Repeated dose oral toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
Caprylyl Gallate	diet	male Wistar albino rats (6 - 8/group)	12 d	0.5%	rats evaluated for liver weight and enzymatic activity; control group given diet without added antioxidant; no other details on treatment provided	mean liver weights and biphenyl 4-hydroxylase activity similar to controls mean liver weight in treated group: 5.1 g/100 g body control liver weight: 5.6 g/100 g mean biphenyl 4-hydroxylase activity: 2.01 µM/g liver/h control biphenyl 4-hydroxylase activity: 1. 93 µM/g liver/h	[27]
Caprylyl Gallate	diet	male Sprague-Dawley rats (5/group)	14 d	1%	rats killed at the end of treatment period and liver weights taken; control animals given unsupplemented diet	mean liver weight similar to untreated controls mean liver weight in treated group: 4.39 ± 0.11 g/100 g bw control liver weight: 4.31 ± 0.24 g/100 g bw	[28]
Dodecyl Gallate	diet	male Sprague-Dawley rats (5/group)	14 d	1%	rats killed at the end of treatment period and liver weights taken; control animals given unsupplemented diet	mean liver weight statistically significantly higher in treated versus animals versus untreated controls mean liver weight in treated group: 5.30 ± 0.22 g/100 g bw control liver weight: 4.31 ± 0.24 g/100 g bw	[28]
Propyl Gallate (purity > 98%)	diet	B6C3F1 mice (10/sex/dose)	13 wk	0, 800, 1500, 3000, 6000, 12,500 ppm	dose-finding study; OECD TG 408; mice killed at end of treatment period and evaluated for survival and microscopic pathological changes following treatment; controls given unsupplemented diet	all animals survived treatment; no microscopic pathological effects observed	[4]
Propyl Gallate	diet	male Sprague-Dawley rats (5/group)	14 d	1%	rats killed at the end of treatment period and liver weights taken; control animals given unsupplemented diet	mean liver weight similar to untreated controls mean liver weight in treated group: 4.43 ± 0.19 g/100 g bw control liver weight: 4.31 ± 0.24 g/100 g bw	[28]
Propyl Gallate (purity > 98%)	diet	Wistar rats (10/sex/group)	90 d	0, 490, 1910, and 7455 mg/kg feed	OECD TG 408; rats killed at end of treatment period and evaluated for survival, body weight, hematological parameters, organ weights, and liver enzyme activity; controls given unsupplemented diet	at the highest dose, reduced body weight gain, hematological changes (reduction of hemoglobin concentration), decreased adrenal weights (in males only), and changes in liver enzyme activity (increase in conjugative enzymes) observed (all reported effects as compared to control) NOAEL was identified as 1910 mg/kg feed, corresponding to approximately 135 mg/kg bw/d.	[4]

OECD = Organisation for Economic Cooperation and Development; TG = test guidelines

Table 6. Developmental and reproductive toxicity studies

Test Article	Vehicle	Test System	Dose/Concentration	Procedure	Results	Reference
IN VITRO						
Propyl Gallate	DMSO and potassium-modified simplex optimized medium	2-cell stage embryos from ICR mice (60 – 95 embryos/ group)	0, 25, 50, or 75 μM used with embryo development; all other evaluations occurred at 0 and 50 μM	fertilized eggs collected from superovulated mice; zygotes with 2 pronuclei were cultured and treated with test substance for 24 – 48 h to assess development to 2-cell and 4-cell stages; negative controls treated with solvent parameters evaluated: -embryo development (proportion of embryos reaching 2-cell and 4-cell stage) -reactive oxygen species (measured via dihydroethidium staining) -DNA damage (assessed via γ-H2A.X immunofluorescence in the nuclei of 2-cell embryos) -mitochondrial distribution and function -lysosomal function -autophagy (measured by evaluating immunofluorescence intensity in cytoplasm) -epigenetic modification (evaluation of DNA methylation and histone methylation levels via immunostaining)	exposure at 50 and 75 μM resulted in a statistically significant reduction in the proportion of embryos reaching the 2-cell stage compared to vehicle-treated controls, and no embryos developed to the 4-cell stage at 25 or 50 μM Propyl Gallate (50 μM) treatment induced oxidative stress, DNA damage, mitochondrial and lysosomal dysfunction, increased autophagy, and altered epigenetic modification in a statistically significant manner compared to controls	[30]
Propyl Gallate	DMSO	oocytes from Kunming mice	0, 150, 200 and 250 μM used to evaluate oocyte meiotic maturation and survival; all other evaluations occurred at 0 and 200 μM	oocytes collected from pregnant mice pre-treated with mare serum gonadotropin; oocytes cultured for 0, 8, and 12 h corresponding to the GV stage, metaphase I stage, and metaphase II stage, respectively; vehicle-treated controls parameters evaluated: -oocyte meiotic maturation and survival (evaluated via the percentage of the first PBE after GV-staged oocytes) -reactive oxygen species (measured via dihydroethidium staining) -early apoptotic oocytes -mitochondrial distribution	Propyl Gallate caused a statistically significant reduction in first PBE at 150 and 200 μM with complete oocyte degeneration at 250 μM compared to vehicle-treated controls at 200 μM, oocytes exhibited statistically significant increases in spindle disorganization, chromosome misalignment, mitochondrial dysfunction, apoptosis, and DNA damage relative to controls	[29]
ANIMAL						
Intraperitoneal Injection						
Propyl Gallate	DMSO	male C57BL/6 mice (20/group)	0 or 50 mg/kg	animals administered either an intraperitoneal injection of Propyl Gallate or DMSO once every 3 d for 4 wk; after treatment, mice killed and testis tissue evaluated for testicular dysfunction, mRNA expression, hormone signaling, and transcriptional regulation	no significant difference in testes weight noted between treated and control animals; statistically significant decrease of expression levels of cyclin D1 and cyclin E1, compared to controls; genes related to hormone receptors and transcriptional factors (luteinizing hormone receptor, epidermal growth factor receptor, androgen receptor, inhibin alpha, and JunD) were statistically significantly decreased compared to controls, except for follicle-stimulating hormone receptor, which was statistically significantly increased compared to controls	[31]

Table 6. Developmental and reproductive toxicity studies

Test Article	Vehicle	Test System	Dose/Concentration	Procedure	Results	Reference
ZEBRAFISH EMBRYO ASSAY						
Propyl Gallate	NR	fertilized zebrafish (*Danio rerio)* embryos (approximately 200 embryos/ group)	1, 10, or 50 ppm	embryos injected with test substance and monitored through 96 h post-fertilization; control groups included both water-injected and non-injected embryos; survival, hatching, and morphological development were assessed, along with whole-larvae measurements of reactive oxygen species and apoptosis	survival remained above 80% in all groups, with no statistically significant differences compared to controls; Propyl Gallate accelerated hatching at 1 and 10 ppm and delayed hatching at 50 ppm; statistically significant increases in developmental malformations (including pericardial edema, yolk sac edema, body malformations, and spinal curvature) were observed at 10 and 50 ppm, relative to controls; Propyl Gallate exposure also produced dose-dependent increases in reactive oxygen species accumulation and apoptotic cell signaling in larvae	[32]

DMSO = dimethyl sulfoxide; DNA = deoxyribonucleic acid; GV = germinal vesicle; mRNA = messenger ribonucleic acid; NR = not reported; PBE = polar body extrusion

Table 7. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
IN VITRO						
Gene Mutation						
Propyl Gallate	DMSO	up to 500 µg/plate	*S. typhimurium* TA92, TA1535, TA100, TA1537, TA94, and TA98	Ames assay; performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic; controls gave expected results	[33]
Propyl Gallate (purity > 98%)	ethanol	10, 33, 100, 333, and 1000 µg/plate	*S. typhimurium* strains TA98, TA100, TA1535, and TA1537	Ames assay; performed with and without metabolic activation; appropriate positive and negative controls used	non-mutagenic; controls gave expected results	[34]
Propyl Gallate	DMSO	0, 0.5, 1, 2, 4, 5, 12.5, 25, 50, 75, 100, 125, 200, 250, 300, 500, and 1000 µg/ml	L5178Y tk+/- mouse lymphoma cells	mouse lymphoma cell forward mutation assay; 6-part experiment; evaluated without metabolic activation; appropriate positive and negative controls used	mutagenic; statistically-significant positive results observed at all tested concentrations; controls gave expected results	[35]
Chromosomal Damage						
Caprylyl Gallate	ethanol	0.031, 0.063, 0.125, 0.250, and 0.500 µg/ml	human peripheral blood lymphocytes	SCE assay; 24- and 48-h exposure; performed without metabolic activation; appropriate positive and negative controls used	statistically-significant, dose-dependent increase in SCE frequency at ≥ 0.125 µg/ml (24 h) and ≥ 0.063 µg/ml (48 h), compared to solvent control	[36]
Caprylyl Gallate	ethanol	0.031, 0.063, 0.125, 0.250, 0.500 µg/ml	human peripheral blood lymphocytes	chromosomal aberration assay; 24- and 48-h exposure; performed without metabolic activation; appropriate positive and negative controls used	non-clastogenic; controls gave expected results	[36]
Caprylyl Gallate	ethanol	0.031, 0.063, 0.125, 0.250, and 0.500 µg/ml	human peripheral blood lymphocytes	cytokinesis-block micronucleus assay; cytochalasin B used to block cytokinesis; binucleated cells scored for micronuclei, nucleoplasmic bridges, and nuclear buds; nuclear division index evaluated; performed without metabolic activation; appropriate positive and negative controls	non-clastogenic; no statistically-significant increases in micronuclei, nucleoplasmic bridges, or nuclear buds compared to solvent control; nuclear division index unchanged	[36]

Table 7. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
Caprylyl Gallate	ethanol	0.031, 0.063, 0.125, 0.250, and 0.500 µg/ml	human peripheral blood lymphocytes	micronucleus-fluorescence in situ hybridization assay; pan-centromeric probes applied to binucleated cells to distinguish centromere-positive and -negative micronuclei; performed without metabolic activation; appropriate positive and negative controls used	non-clastogenic; no statistically-significant increase in centromere-positive or centromere-negative micronuclei compared to solvent control	[36]
Propyl Gallate	DMSO	0, 0.5, 1.6, 3, 5, 7.5, 10, 16, 50, and 160 µg/ml	CHO cells	SCE assay; performed with and without metabolic activation; appropriate positive and negative controls used	mutagenic; statistically-significant increases in SCE without presence of metabolic activation at concentrations ≥ 5 µg/ml; increase also noted with metabolic activation at concentrations ≥ 50 µg/ml; controls gave expected results	[37]
Propyl Gallate	saline	up to 40 µg/ml	Chinese hamster lung fibroblasts	chromosomal aberration assay; performed without metabolic activation; appropriate negative control used	clastogenic; controls gave expected results	[33]
Propyl Gallate	DMSO	without metabolic activation: 0, 1, 2, 5, 16, 30, and 50 µg/ml with metabolic activation: 0, 300, 400, and 500 µg/ml	CHO cells	chromosomal aberration assay; performed with and without metabolic activation; appropriate positive and negative controls used	mutagenic; at doses ≥ 5 µg/ml, dose-dependent, statistically-significant increases in chromosomal aberrations observed, in the absence of metabolic activation; no positive results observed in presence of metabolic activation; controls gave expected results	[37]
Propyl Gallate	DMSO	experiment 1: 0, 3, 5, and 7 µg/ml experiment 2: 0, 4, 8, and 12 µg/ml	Chinese hamster lung fibroblasts (V79)	2-part micronucleus assay; 3h incubation; performed without metabolic activation; vehicle control	mutagenic; statistically-significant micronucleus induction observed at concentrations ≥ 5 µg/ml in experiment 1 and ≥ 8 µg/ml in experiment 2; vehicle control gave expected results	[38]
Propyl Gallate	DMSO	experiment 1: 0, 11.5, 23.5, and 48 µg/ml experiment 2: 0, 8.1, 23.5, and 33.6 µg/ml	Chinese hamster lung cells	2-part micronucleus assay; 3h incubation; performed without metabolic activation; vehicle control	mutagenic; statistically-significant micronucleus induction observed at concentrations 48 µg/ml in experiment 1 and ≥ 23.5 µg/ml in experiment 2; vehicle control gave expected results	[38]
Propyl Gallate	DMSO	experiment 1: 0, 5.6, 10, and 13.3 µg/ml experiment 2: 0, 10, and 15 µg/ml	CHO cells	2-part micronucleus assay; 3h incubation; performed without metabolic activation; vehicle control	mutagenic; statistically-significant micronucleus induction observed at concentrations ≥ 10 µg/ml in experiment 1 and 2; vehicle control gave expected results	[38]
Propyl Gallate	DMSO	experiment 1: 0, 40, 95, and 225 µg/ml experiment 2: 0, 10, 15, and 17.5 µg/ml	human peripheral blood lymphocytes	2-part micronucleus assay; 3h incubation; performed without metabolic activation; vehicle control	non-mutagenic; vehicle control gave expected results	[38]
Propyl Gallate	DMSO	experiment 1: 0, 4.2, 5.6, and 31.6 µg/ml experiment 2: 0, 13, 20.5, and 50 µg/ml	TK6 human lymphoblastoid cells	2-part micronucleus assay; 3h incubation; performed without metabolic activation; vehicle control	mutagenic; statistically-significant micronucleus induction observed at concentrations ≥ 4.2 µg/ml in experiment 1 and ≥ 20.5 µg/ml in experiment 2; vehicle control gave expected results	[38]

Table 7. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
Propyl Gallate	DMSO	experiment 1: 0, 490, 700, and 1000 µg/ml experiment 2: 0, 85.6, 122, and 1485 µg/ml	HepG2 cells	2-part micronucleus assay; 3h incubation; performed without metabolic activation; vehicle control	equivocal; no statistically-significant micronucleus induction observed in experiment 1; statistically-significant micronucleus response observed at 1485 µg/ml in experiment 1; however, number of cells scored was < 200; vehicle control gave expected results	[38]
			DNA Strand Breaks			
Caprylyl Gallate	ethanol	0.031, 0.063, 0.125, 0.250, and 0.500 µg/ml	human peripheral blood lymphocytes	alkaline comet assay; 1-h exposure; performed without metabolic activation; appropriate positive and negative controls used	non-genotoxic; controls gave expected results	[36]
Caprylyl Gallate	NR	0, 100, 500, 1000, 2000, and 5000 µM	human peripheral blood lymphocytes	alkaline comet assay; 1-h exposure; performed without metabolic activation; appropriate positive and negative controls used	genotoxic; statistically-significant increase in DNA migration in comet tails observed at all concentrations, compared to negative control; controls gave expected results	[39]
Propyl Gallate	serum-free medium	0, 150, 250, and 500 µM	human fibroblasts cell line GM05757	alkaline elution assay; 1-h incubation; performed without metabolic activation; vehicle control	non-genotoxic; control gave expected results	[40]
Propyl Gallate	filtered media and DMSO	0 and 1000 µM	A549 human lung cancer cells	alkaline comet assay; performed without metabolic activation; appropriate positive and negative controls used	genotoxic; statistically significant DNA damage observed in treated versus negative control cells	[41]
Propyl Gallate	water	0, 15.6, 62.5, and 250 µM	mouse embryonic stem cells	modified alkaline comet assay; cells exposed to test substance followed by hydrogen peroxide to induce DNA strand breaks; performed without metabolic activation; appropriate positive and negative controls used	non-genotoxic; test substance did not induce genotoxicity via DNA cross formation; positive control gave expected results; results on negative control not stated	[4]
			IN VIVO			
			Chromosomal Damage			
Propyl Gallate	corn oil	0, 75, 150, and 300 mg/kg bw/d	male B6C3F1 mice (5/group)	mouse bone marrow micronucleus assay; intraperitoneal administration daily for 3 d; bone marrow samples obtained 24 h after final exposure; appropriate positive and negative controls used	non-mutagenic; controls gave expected results	[42]
Propyl Gallate	DMSO	0 and 217 mg/kg bw/d	female B6C3F1 mice (5/group)	mammalian erythrocyte micronucleus test; intraperitoneal injection for 2 d at 24-h intervals; samples collected 24, 48, and 72 h, and in some cases at 0 and 96 h, post-administration; 500 polychromatic erythrocytes evaluated in each mouse; tests occurred with test substance alone, with test substance + DMBA pretreatment, and DMBA alone (test performed to evaluate the potential genotoxic inhibitory effect of Propyl Gallate)	non-genotoxic; cells treated with Propyl Gallate alone did not result in an increased frequency of micronuclei; treatment with DMBA resulted in an expected increase in frequency of micronuclei; treatment with Propyl Gallate in DMBA-pre-treated cells did not cause any significant inhibitory effect	[43]
			DNA Strand Breaks			
Propyl Gallate	0.9% sodium chloride in water	0, 500, 1000, and 2000 mg/kg bw/d	male Wistar Han rats (5/group)	mammalian alkaline comet assay; OECD TG 489; animals treated with test substance via gavage; dosing time: 0 and 21 h; sampling time: 3 – 4 h after last treatment; glandular stomach, liver, duodenum, and testis cells collected for DNA damage; appropriate positive and negative controls used	non-genotoxic; controls gave expected results	[4]

Table 7. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
Propyl Gallate	olive oil	2000 mg/kg bw	male ddY mice (4/group)	mammalian alkaline comet assay; animals administered test substance orally (method of oral administration not stated; single administration); animals killed 3 or 24 h after treatment; DNA damage evaluated in stomach, liver, kidney, bladder, lung, brain, and bone marrow cells; solvent control used	non-genotoxic; negative control gave expected results	[44]

CHO = Chinese hamster ovary; DMBA = dimethylbenzanthracene; DMSO = dimethyl sulfoxide; DNA = deoxyribonucleic acid; HepG2 = human liver cell line; OECD = Organisation for Economic Cooperation and Development; SCE = sister chromatid exchange; TG = test guidelines

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration /Dose	Test Population/System	Protocol	Results	Reference
IRRITATION						
IN VITRO						
Propyl Gallate	none	10 ± 2 mg/tissue	reconstructed human epidermis (3 replicates/group)	OECD TG 439; reconstructed human epidermis test method; test substance applied for 15 min followed by a 42-h post-exposure incubation; mean relative tissue viability assessed via MTT assay; appropriate positive and negative controls used	non-irritating mean tissue viability = 70.3% (substances with values > 50% are classified as non-irritants)	[4]
SENSITIZATION						
IN VITRO						
Propyl Gallate (purity ≥ 99%)	NR	1 and 2%	reconstructed human epidermis and THP-1 human monocytic cell line	reconstructed human epidermis-THP-1 coculture model developed for method evaluation; Propyl Gallate used as positive sensitization control; cells exposed to test substance for 24 h; sensitization potential was assessed via cluster of differentiation 54 and 86 (CD54/CD86) expression and interleukin-18 (IL-18) release; formulations meeting relative fluorescence intensity for CD 86 ≥200, CD 54 ≥150, or IL-18 ≤ 0.79 were flagged as potential sensitizers	showed responses consistent with sensitizer controls	[61]
ANIMAL						
Dodecyl Gallate	DMSO	1, 10, 25, and 50%; 25µl	CBA female mice (number not stated)	LLNA; daily topical application to the dorsal surface of each ear for 3 d; control mice treated with vehicle only; 5 d after first topical application, all mice were injected with tritiated thymidine and killed 5 h later; lymph nodes excised and SI calculated; control information not stated	sensitizing at all test concentrations SI at 1%: 12.1 SI at 10%: 29.7 SI at 25%: 29.3 SI at 50%: 36 (values ≥ 3 indicate a positive response)	[62]
Propyl Gallate	saline	induction injection: 0.35% induction patch: 25% challenge patch: 5%	Dunkin Hartley guinea pigs (number and sex not stated)	guinea pig maximization assay; 6 induction injections; after 6 – 8 d, a 48-h occlusive induction patch applied; 12 – 14 d later, 24-h occlusive challenge patch applied; use of controls not stated	sensitizing at all concentrations; 100% of tested animals showed positive response	[63]

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration /Dose	Test Population/System	Protocol	Results	Reference
Propyl Gallate	acetone and olive oil	5, 10, and 25%; 25µl	4 CBA/Ca mice/group (sex not stated)	LLNA; daily topical application to the dorsal surface of each ear for 3 d; control mice treated with vehicle only; 4 – 5 d after first topical application, all mice were injected with ^{3}HTdR and killed 5 h later; lymph nodes excised and stimulation index calculated	sensitizing at all test concentrations; all concentrations produced stimulation indices > 3, indicating a positive response	63
				HUMAN		
Caprylyl Gallate	petroleum	0.25%	201 healthy subjects*	occlusive patch test on cosmetic series of allergens; results recorded at day 2 and 4	0% positivity rate	64
Dodecyl Gallate	petroleum	0.25%	201 healthy subjects*	occlusive patch test on cosmetic series of allergens; results recorded at day 2 and 4	1.5% positivity rate	64
Propyl Gallate	petroleum	1%	201 healthy subjects*	occlusive patch test on cosmetic series of allergens; results recorded at day 2 and 4	0% positivity rate	64

CD54 = cluster of differentiation 54; CD86 = cluster of differentiation 86; DMSO = dimethyl sulfoxide; [^{3}H]methyl thymidine = ^{3}HTdR; IL-18 = interleukin-18; LLNA = local lymph node assay; MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; NR = not reported; OECD = Organisation for Economic Cooperation and Development; SI = stimulation index; TG = test guidelines; THP-1 = human monocytic leukemia cell line

*healthy university students from Beijing were recruited for this assay; it should be noted that knowledge or suspicion of an existing allergy was neither an inclusion or exclusion category

Table 9. Retrospective and Prospective Studies

Ingredient	Patients	Time Frame	Methods/Details	Results	Reference
			RETROSPECTIVE STUDIES		
Caprylyl Gallate	2968 patients attending contact dermatitis and occupational dermatology clinic	1995 - 2010	retrospective study of dermatitis patients evaluating data from 1995 - 2010; 48-h occlusive patch tests using 0.25% Caprylyl Gallate in petroleum	200 patients (6.7% of patients) showed positive responses	73
Caprylyl Gallate	83 dermatitis patients	1997 - 2006	retrospective study evaluating data of patch test patients who returned for delayed readings between day 7 – 10 or beyond; this cohort was predominantly patients with suspected allergies to metals and corticoid steroids; patch testing with 0.25% Caprylyl Gallate (vehicle not stated)	number of positive patients: -negative day 5, negative day ≥ 7: 72 patients -negative day 5, positive day ≥ 7: 0 patients -positive day 5, negative day ≥ 7: 7 patients -positive day 5, positive day ≥ 7: 1 patient	67
Caprylyl Gallate	75 dermatitis patients	2000 - 2007	retrospective study evaluating clinical database results regarding positive reactions to skin care product allergens between 2000 – 2007; patch test using 0.25% Caprylyl Gallate (vehicle not stated)	16% positive response rate	70
Caprylyl Gallate	41 patients with allergic contact cheilitis	2001 - 2011	retrospective study evaluating patients with non-acitinic cheilitis who underwent patch testing between 2001 and 2011; patients underwent patch testing of several series including 48-h occlusive patch test using 0.25% Caprylyl Gallate (vehicle not stated)	6 patients (14.6% of patients) showed positive responses	77
Caprylyl Gallate	245 patients with allergic contact dermatitis	2017 - 2020	retrospective study evaluating patch tests results of patients tested with supplemental screening series including 48-h occlusive patch test to 0.25% Caprylyl Gallate in petroleum	9 patients (3.7% of patients) showed positive reactions	68
Caprylyl Gallate and Dodecyl Gallate	89 patients with burning mouth syndrome and allergic patch test reactions	2008 - 2012	retrospective study; patch testing with North American Standard tray, dental tray, and cheilitis tray, including Caprylyl Gallate (0.3%) and Dodecyl Gallate (0.3%) (vehicles not stated); 48-h occlusive patch tests	positive responses to Caprylyl Gallate: 16 (18% of patients) positive responses to Dodecyl Gallate: 25 (28% of patients)	74

Table 9. Retrospective and Prospective Studies

Ingredient	Patients	Time Frame	Methods/Details	Results	Reference
Caprylyl Gallate, Dodecyl Gallate, and Propyl Gallate	1173 patients with allergic contact dermatitis	1985 - 2006	retrospective study of patch test cases diagnosed at a dermatology allergy unit (1985 – 2006); patch test using preservative/cosmetic and bakery series including 48-h occlusive patch tests using 0.25% Caprylyl Gallate, 0.25% Dodecyl Gallate, and 1% Propyl Gallate (all in petroleum)	overall sensitization rate: 3.92% of patients distribution of positive reactions: -Caprylyl Gallate: 27 patients (58.7% of patients) -Dodecyl Gallate: 6 patients (13% of patients) -Propyl Gallate: 30 patients (65.2% of patients) 34.8% of patients reacted to more than 1 gallate primary sources of sensitization were lip products and bakery products	[75]
Dodecyl Gallate	3418 patients attending contact dermatitis and occupational dermatology clinic	1995 - 2010	retrospective study of dermatitis patients evaluating data from 1995 - 2010; 48-h occlusive patch tests using 0.25% Dodecyl Gallate in petroleum	240 patients (7% of patients) showed positive responses	[73]
Dodecyl Gallate	105 dermatitis patients	1997 - 2006	retrospective study evaluating data of patch test patients who returned for delayed readings between d 7 – 10 or beyond; this cohort was predominantly patients with suspected allergies to metals and corticoid steroids; patch test using 0.25% Dodecyl Gallate (vehicle not stated)	number of positive patients: -negative day 5, negative day ≥ 7: 89 patients -negative day 5, positive day ≥ 7: 6 patients -positive day 5, negative day ≥ 7: 6 patients -positive day 5, positive day ≥ 7: 4 patients	[67]
Dodecyl Gallate	937 dermatitis patients	2000 - 2007	retrospective study evaluating clinical database results regarding positive reactions to skin care product allergens between 2000 – 2007; patch test using 0.25% Dodecyl Gallate (vehicle not stated)	9.2% positive response rate	[70]
Dodecyl Gallate	1927 patients with chronic eczema	2001 - 2006	patch testing performed in patients from 2001 – 2006; 48-occlusive patch test using common excipients of topical preparations and cosmetics including 0.3% Dodecyl Gallate in petroleum	2% positive response rate	[71]
Dodecyl Gallate	41 patients with allergic contact cheilitis	2001 - 2011	retrospective study evaluating patients with non-acitinic cheilitis who underwent patch testing between 2001 and 2011; patients underwent patch testing of several series including 48-h occlusive patch test using 0.25% Dodecyl Gallate (vehicle not stated)	9 patients (22% of patients) showed positive responses	[77]
Dodecyl Gallate	341 allergic contact dermatitis patients	2001 - 2020	retrospective study evaluating data of patch test patients who had patch test readings performed at greater than day 8 (late delayed positive reactions); data evaluated from 2001 – 2020; patch test with 0.25% Dodecyl Gallate (vehicle not stated)	11 patients (3.2% of patients) had late delayed positive reactions	[69]
Dodecyl Gallate	2868 patients with cosmetic allergy	2005 - 2019	retrospective study evaluating data from 2005 – 2019 regarding patch tests; patients patch tested with antimicrobials, vehicles, and cosmetics series including 48-h occlusive patch test on 0.25% Dodecyl Gallate in petroleum	44 patients (1.5% of patients) showed positive reaction	[72]
Dodecyl Gallate	61 patients with diagnosed allergic contact cheilitis	2012 - 2017	retrospective study; patch testing with Australian baseline series and allergens relevant to allergic contact cheilitis, including Dodecyl Gallate (0.25% in petroleum); 48-h occlusive patch tests	6 patients (9.8% of patients) showed positive responses	[65]
Dodecyl Gallate	245 patients with allergic contact dermatitis	2017 - 2020	retrospective study evaluating patch tests results of patients tested with supplemental screening series including 48-h occlusive patch test on 0.25% Dodecyl Gallate in petroleum	17 patients (6.9% of patients) showed positive reactions	[68]
Propyl Gallate	5908 patients with allergic contact dermatitis in 1988 – 1996; 3621 patients with contact allergic contact dermatitis in 1997 - 2005	1988 – 1996 and 1997 – 2005	evaluation of patch testing during different time periods (1988 – 1996 and 1997 – 2005) to evaluate if increase in positive patch tests rates to Propyl Gallate prevalent; 48-h occlusive patch test using 1% Propyl Gallate in petroleum	positive response in 1988 – 1996: 0.45% positive response in 1997 – 2005: 0.77% a statistically significant increase in positive rates observed	[78]

Table 9. Retrospective and Prospective Studies

Ingredient	Patients	Time Frame	Methods/Details	Results	Reference
Propyl Gallate	2773 patients attending contact dermatitis and occupational dermatology clinic	1995 - 2010	retrospective study of dermatitis patients evaluating data from 1995 - 2010; 48-h occlusive patch tests using 1% Propyl Gallate in petroleum	46 patients (1.7%) showed positive responses	[73]
Propyl Gallate	104 dermatitis patients	1997 - 2006	retrospective study evaluating data of patch test patients who returned for delayed readings between d 7 – 10 or beyond; this cohort was predominantly patients with suspected allergies to metals and corticoid steroids; patch test using 1% Dodecyl Gallate (vehicle not stated)	number of positive patients: -negative day 5, negative day ≥ 7: 100 patients -negative day 5, positive day ≥ 7: 2 patients -positive day 5, negative day ≥ 7: 1 patient -positive day 5, positive day ≥ 7: 1 patient	[67]
Propyl Gallate	943 dermatitis patients	2000 - 2007	retrospective study evaluating clinical database results regarding positive reactions to skin care product allergens between 2000 – 2007; patch test using 1% Propyl Gallate (vehicle not stated)	0.7% positive response rate	[70]
Propyl Gallate	1927 patients with chronic eczema	2001 – 2006	patch testing performed in patients from 2001 – 2006; 48-h occlusive patch test using common excipients of topical preparations and cosmetics including 0.5% Propyl Gallate in petroleum	0.3% positive response rate	[71]
Propyl Gallate	41 patients with allergic contact cheilitis	2001 - 2011	retrospective study evaluating patients with non-acitinic cheilitis who underwent patch testing between 2001 and 2011; patients underwent patch testing of several series including 48-h occlusive patch test using 1% Propyl Gallate (vehicle not stated)	1 patient (2.4% of patients) showed positive responses	[77]
Propyl Gallate	2868 patients with cosmetic allergy	2005 - 2019	retrospective study evaluating data from 2005 – 2019 regarding patch tests; patients patch tested with antimicrobials, vehicles, and cosmetics series including 48-h occlusive patch test on 1% Propyl Gallate in petroleum	13 patients (0.45% of patients) showed positive reaction	[72]
Propyl Gallate	245 patients with allergic contact dermatitis	2017 - 2020	retrospective study evaluating patch tests results of patients tested with supplemental screening series including 48-h occlusive patch test to 1% Propyl Gallate in petroleum	2 patients (0.8% of patients) showed positive reactions	[68]
PROSPECTIVE STUDIES					
Caprylyl Gallate	103 patients with rosacea and 104 control subjects	2014 - 2017	prospective monocenter study; patients investigated for contact sensitization via patch testing cosmetic series including 48-h occlusive patch using 0.25% Caprylyl Gallate in petroleum	11 positive reactions in rosacea patients (10.7% of patients); 4 positive reactions in control subjects (3.8% of patients)	[66]
Caprylyl Gallate and Propyl Gallate	8 patients with contact cheilitis	not stated	-duration of contact cheilitis symptoms ranged from 1 wk – 3 mo -all patients used cosmetics -patch testing performed with a cosmetic series including Caprylyl Gallate and Propyl Gallate (concentrations and vehicles not stated); occlusive test	1 patient (12.5% of patients) showed a positive response to Caprylyl Gallate and Propyl Gallate	[76]
Dodecyl Gallate	103 patients with rosacea and 104 control subjects	2014 - 2017	prospective monocenter study; patients investigated for contact sensitization via patch testing cosmetic series including 48-h occlusive patch using 0.25% Dodecyl Gallate in petroleum	9 positive reactions in rosacea patients (8.7% of patients); 4 positive reactions in control subjects (3.8% of subjects)	[66]
Dodecyl Gallate	80 patients with contact dermatitis and 80 control subjects	2023 - 2024	cross-sectional study; patch testing performed using an extended panel of supplemental allergens including 0.25% Dodecyl Gallate in petroleum; 48-h occlusive test	16 positive reactions in dermatitis patients (20% of patients); 6 positive reactions in control subjects (7.5% of subjects)	[79]
Propyl Gallate	103 patients with rosacea and 104 control subjects	2014 - 2017	prospective monocenter study; patients investigated for contact sensitization via patch testing cosmetic series including 48-h occlusive patch using 1% Propyl Gallate in petroleum	0 positive reactions in rosacea patients; 0 positive reactions in control subjects	[66]

Table 10. Allergic reactions to gallates in humans (consumer and occupational case reports)

Ingredient	Patient	Details	Reference
Consumer Case Reports			
Caprylyl Gallate	37-yr-old woman	-acute cheilitis associated with lipstick for several years -patch testing with European standard series, series of preservatives, emulsifying excipients, fragrances, and photoprotectors showed no positive responses -patch testing with lipstick resulted in a positive response -patch tests with Caprylyl Gallate (a component of the lipstick; tested at 0.3% in petroleum) yielded positive results -additional tests with other gallates (Dodecyl Gallate (0.3% in petroleum) and Propyl Gallate (0.5% in petroleum) were negative -patient completely recovered after stopping lipstick use	82
Caprylyl Gallate and Dodecyl Gallate	54-yr-old woman	-5 yr history of recurrent lip swelling -positive patch testing to 0.3% Caprylyl Gallate (in petroleum) and 0.3% Dodecyl Gallate (in petroleum) -marked reduction in episodes after avoiding foods and lip preparations containing gallates	83
Dodecyl Gallate	42-yr-old woman	-beauty therapist presented with skin rashes on face and neck after a facial; patient also presented with a strange feeling on the tongue -patch tests using an extended European patch test series, a cosmetics series, some fragrances, hairdressing chemicals, and approximately 20 of her own samples -patient tested positive for Dodecyl Gallate -patient was advised to avoid dietary gallates and reported improvement of symptoms	73
Propyl Gallate	30-yr-old woman	-itchy and painful rash on lips following use of lip balm containing Propyl Gallate -patch test with North American Contact Dermatitis Group (NACDG) standard series, preservative, fragrance, bakery, hair, and sunscreen series -positive reactions observed for Propyl Gallate, (as well as Caprylyl Gallate, cobalt chloride, bacitracin, fragrance mixes I and II, and nickel sulfate) -lip dermatitis resolved after avoiding lip balm use	84
Propyl Gallate	49-yr-old woman	-recurrent episodes of dermatitis and systemic symptoms -first episode occurred 24 h after sunscreen application; after this application, patient experience pruritic eruption on arms and neck, phlegm, tachycardia – patient hospitalized -ultraviolet A photo-testing yielded normal results -patch testing with NACDG standard panel, supplemental panels, photo patch, and personal care products -2 h after application of test patches, patient had difficulty swallowing and racing heart, and received oral treatment at emergency department -24-h patch testing revealed positive results to fragrance mix I, 2(2-hydroxy-5-methylphenyl)benzotriazole, and triclosan (no positive reaction to Propyl Gallate) -at day 4 final reading, while patient was on prednisone, symptoms resolved, and the only positive reaction was to Propyl Gallate -results were interpreted as immediate urticarial reactions to benzophenones and a delayed reaction to Propyl Gallate	85
Propyl Gallate	29-yr-old woman	-1 -2 mo history of recurrent history and vesiculation of lips previously incorrectly diagnosed as herpes labialis, but worsened with topical treatment of acyclovir in a propylene glycol base -occlusive patch testing performed with herpes labialis treatments, and propylene glycol – positive results obtained for acyclovir cream and propylene glycol -2 wk later, patient presented with acute cheilitis and erythema, swelling, and vesiculation, with no history of using acyclovir cream or products containing propylene glycol -further patch testing performed using European standard series and with patients' cosmetics and personal care products, including Propyl Gallate (0.5% in petroleum); 48-h occlusive patches -patient had positive response to lipstick (containing Propyl Gallate but no propylene glycol), and to Propyl Gallate	86
Propyl Gallate	58-yr-old woman	-1-yr history of dermatitis localized to the fingertips of the first 3 fingers of both hands -dermatitis responded well to phototherapy but re-occurred 1 wk after discontinuing therapy -patient reported handling fish food 2 - 3 x/d -patch testing performed using American Contact Dermatitis Society core series, cosmetic series, and the patient's new liquid bandage -positive results observe for ethyl cyanoacrylate, Caprylyl Gallate (0.25% in petroleum), and Propyl Gallate (1% in petroleum) -it was discovered that the fish food containing Propyl Gallate; symptoms improved gradually after handling fish food with gloves	87
Propyl Gallate	56-yr-old woman	-7-mo history of persistent facial dermatitis characterized by pruritis, erythema, and scaling -patient reported symptoms corresponding to acquiring a pet rabbit -patch testing performed using baseline series of the Spanish Research Group on Contact Dermatitis and Skin Allergy, a specific plant series, thimerosal, and benzalkonium chloride; 48-h occlusive patches -positive results observed for Propyl Gallate (1% in petroleum) and nickel sulfate -patient identified Propyl Gallate (5 mg/kg) in the rabbit food -avoidance of this food additive let to complete resolution of symptoms	88

Table 10. Allergic reactions to gallates in humans (consumer and occupational case reports)

Ingredient	Patient	Details	Reference
Propyl Gallate	62-yr-old man	-20-yr history or seborrheic dermatitis; presented with worsening dermatitis -patch test with Italian society of Allergological, Occupational, and Environmental Dermatology standard series and corticosteroid series -patient had strong reactions to several corticosteroids -patient discontinued use of topical corticosteroids, and used steroid-free cream; however, after 6 mo, patient presented with flare of facial dermatitis -patch testing with the steroid-free cream resulted in positive results -patch testing on individual ream ingredients performed; positive results observed for Propyl Gallate (1% in Propyl Gallate) and pentylene glycol	89
Occupational Case Reports			
Caprylyl Gallate	19-yr-old food worker	-mixed Caprylyl Gallate powder with heated chicken fat for first time while wearing plastic gloves, no other preventative measures -that night, patients had nausea, itchy swollen hands, face, and legs that lasted for 1 wk and healed spontaneously -patient again performed same work, and had weakness, severe edema of the eyelids, and edema of the legs and belly -patient patch tested with European standard series and Caprylyl Gallate (0.1% in petroleum and 1% in alcohol) -positive patch tests observed for nickel sulfate and both concentrations Caprylyl Gallate -a scratch test with Caprylyl Gallate (1% in alcohol) was negative after 20 min; however, an eczematous reaction later developed	90
Caprylyl Gallate and Dodecyl Gallate	46-yr-old food worker	-dermatitis on hands and face -occupation consisted of mixing peanut butter with Caprylyl Gallate -patch testing with International Contact Dermatitis Research Group standard series, Caprylyl Gallate (0.1 and 1%) in olive oil, and Dodecyl Gallate (0.1 and 1%; vehicle not stated) -results to standard series negative; positive responses to Caprylyl Gallate at both concentrations; negative response to Dodecyl Gallate	81
Dodecyl Gallate	23-yr-old cheese counter assistant	-patient with extremely painful itchy hand dermatitis, characterized by dermatitis sicca -unsuccessfully treated with topical corticosteroids -3-mo history of working as a cheese counter assistant -patch tested with Italian Group for Research on Occupational Dermatoses and Contact Allergies series and food preservatives series, including Dodecyl Gallate (0.1% in petroleum) -strong positive reaction to Dodecyl Gallate -complete recovery after abstaining from cheese counter work and brief therapy with clobetasol propionate	91
Propyl Gallate	41-yr-old industrial worker	-patient presented with marked erythema and edema around the eyes -patient worked at a plant that manufactured a synthetic textile fiber and used Propyl Gallate as a stabilizing agent -the previous day, the patient reported cleaning a device that had powdered Propyl Gallate injected into it -patch tests performed using European standard series together including Propyl Gallate -positive response observed for Propyl Gallate (1% in petroleum) and to an open test to a saturated solution of Propyl Gallate in ethanol -symptoms settled after use of antihistamines and redeployment away from potential sources of Propyl Gallate	92

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