

# Gallates – toxicological data and a pilot study on the prevalence of contact sensitization

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## Abstract

Propyl, octyl- and dodecyl gallates are largely used in food, cosmetic and pharmaceutical industry as additives – preservatives. The main source of exposure non-related with food consumption is their use of cosmetic products. Gallates are classified as skin sensitization human health hazard. This research aims to evaluate the prevalence of contact sensitization to gallates and to estimate the possible cross/concomitant sensitization to gallate mix and other cosmetics ingredients among cosmeticians and cosmetology students. Skin patch testing with Gallate mix along with 19 other haptens was performed among 109 participants – 37 cosmetology students, 26 cosmeticians, and 46 controls. The study established high prevalence of contact sensitization to gallates, with higher risk for students (45.9%) and cosmeticians (38.5%). A significantly higher ( $p = 0.008$ ) prevalence of co-sensitization to decyl glucoside was established for the control group. Proper risk information, with complex programs for prevention of occupational skin diseases should be provided.

## Keywords

contact sensitization, cosmetics, gallates, occupational exposure

## Introduction

Food additives are chemical substances in processed foods, which carry out specific technological functions, e.g. extending food shelf-life and/or improving organoleptic properties such as color, taste, and texture. Antioxidants are one of the most used for food preservation (Marcio et al. 2018).

Gallic acid (GA, 3,4,5-trihydroxy benzoic acid), a core structure of gallates, is a polyphenolic antioxidant naturally produced in fruits, plants, and plant parts (tea leaves, evening primrose, bearberry leaf, blueberries, and walnuts) (Ow and Stupans 2003). Synthetic GA is produced

through alkaline and acid hydrolysis of gallnuts tannins (gallotannin or taratannin) and synthesized from phenylalanine via trihydroxycinnamic acid or caffeic acid (Bajpai and Patil 2008). Propyl, octyl and dodecyl gallates are widely used in food, cosmetic and pharmaceutical industries as additives (E 310, E311, E312) for delaying, retarding or preventing the development of oxidative deterioration (Zurita et al. 2007; European Commission 2011; Gultekin and Dogue 2012; Xu et al. 2021). In cosmetics, gallates are used as an antioxidant to stabilize vitamins, essential oils, perfumes, as well as fats and oils that readily undergo oxidation. Studies have also reported some therapeutic benefits of propyl gallate (chemotherapeutic, nephropro-

tective, and cytotoxic to HeLa cells) (Javaheri-Ghezeldizaj et al. 2023).

Food additives may be detrimental to human health when consumed long-term or at higher doses (Dehghan and Mohammadi 2018). Currently, the Maximum Permitted Levels (MPLs) of propyl gallate individually, or in combination with octyl and dodecyl gallate, tertiary-butyl hydroquinone (TBHQ) and butylated hydroxyanisole (BHA) range from 25 mg/kg in processed potato products to 400 mg/kg in food supplements and chewing gum, according Annex II of Regulation (EC) No 1333/2008, while in the Regulation 2009/1223/EC on cosmetic products there are no restrictions for their use (Regulation (EC) No 1333/2008).

## Exposure

According to the European Food Safety Authority (EFSA) exposure assessment of propyl gallate, the anticipated exposure to propyl gallate (mg/kg bw/day) when used as food additive varies from 0.02–0.10 for elderly people (>65 years) in estimated exposure scenario using MPLs at Mean Values, to 0.16–0.59 mg/kg bw/day for children (3–9 years) in the same scenario at High levels. Data from refined exposure assessment using reported data on analytical levels, supplemented with MPLs, show substantially lower exposure, reaching a maximum of 0.67 mg/kg bw/day for the elderly age group (EFSA 2014).

The main food categories contributing to the dietary exposure of gallates are chewing gum, breakfast cereals, fine bakery wares, herbs, spices and seasonings, soups and broths, sauces, potato-, cereal-, flour- or starch based snacks, processed nuts, and food supplements. It should be noted that the main food category are fine bakery wares for all age groups.

Furthermore, besides foods, the total exposure to propyl, octyl and dodecyl gallate can be attributed to some other sources such as food contact materials (Commission Regulation (EU) No 10/2011). However, the main source of exposure non-related to food consumption is the use of cosmetic products like leave-on products such as skin creams and wash-off products, such as hand and bathing soaps.

## Metabolism and toxicokinetics of propyl gallate

The major routes of exposure to propyl gallate (PG) are inhalation, ingestion, and absorption through the skin (Dehghan et al. 2018; Wang et al. 2019). Studies have demonstrated that administered PG is not easily excreted and may accumulate in the body (Kobayashi et al. 2004). Significant part of the PG is hydrolyzed to GA and propyl alcohol (via the Krebs cycle) in the liver. More than 80% of GA is entirely released into the systemic circulation, and the rest (20%) are metabolized to 4-O-methyl gallic acid (72%), unconjugated phenolic compounds (6.7%), and minor metabolites such as pyrogallol (Javaheri-Ghezeldizaj et al. 2023). The PG molecules can effectively bind to

human serum albumin (HSA) and bovine serum albumin (BSA) distributed within the body (Ezzati et al. 2014).

## Toxicological data

Data indicate low acute and chronic oral toxicity for gallates, with no genotoxic, mutagenic or reproductive effects *in vivo* being observed. However, propyl-, octyl- and dodecyl gallates are classified in Category 1 hazard class for serious eye damage/eye irritation and skin sensitization, according to the harmonized classification – Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation) (ECHA). Furthermore, the skin sensitization potential of gallates was pointed out by the Scientific Committee on Food (SCF) – “Gallates may cause skin sensitization and subsequent exacerbation of the resulting contact dermatitis occurs in some such sensitized individuals after ingestion of gallates.”

The ability of a sensitizer to penetrate epithelium is a very important factor regarding its ability to elicit allergic response, along with the exposure dose, frequency and duration of exposure (Paulsen et al. 2009). Moreover, to explain the chemical mechanism of skin sensitization, it was observed that a chemical must either be inherently protein reactive or be converted (chemically or metabolically) to a protein reactive species, which can associate effectively with proteins, mainly by electrophile-nucleophile reactions (Tier et al. 2007).

When used as an ingredient of cosmetic products, PG acts as an irritant to the skin and eyes and a dermal sensitizer at concentrations of 0.003–10% (Holcomb et al. 2017). PG and other gallates are allergens that present manifestations, such as irritation and allergic contact dermatitis, in susceptible consumers and handlers of products such as lipsticks, sunscreens, and cosmetics (Foti et al. 2010; Holcomb et al. 2017).

The sensitizing capacity of gallates varies according to their different chemical structure, namely increases correspondingly with the length of their alkyl side chain, as dodecyl gallate was found to be the strongest contact sensitizer (Hausen and Bayer 1992). Nevertheless, other multicenter patch test studies indicate that the octyl gallate displays the biggest sensitizing capacity, followed by dodecyl gallate and propyl gallate (Watkins and Zippin 2012). However, as propyl gallate is the most widely used, most of the reported cases of contact dermatitis had been attributed to it (García-Melgares et al. 2007).

Propyl gallate is used in many cosmetic product categories, including lipsticks, bath preparations, miscellaneous; body and hand preparations (excluding shaving preparations); bath capsules; moisturizing preparations; skin-care preparations, misc.; makeup preparations (not eye); eye-makeup preparations, miscellaneous; face and neck preparations (excluding shaving preparations); bath oils, tablets, and salts; cleansing products (cold creams, cleansing lotions, liquids, and pads); eyeliners; night skin care preparations, eye shadows; eye-brow pencils; face powders; foundations; indoor tanning preparations; mascara; suntan gels, creams, and liquids.

Therefore, the aim of the present study is to evaluate the prevalence of contact sensitization to gallates and to estimate the possible prevalence of cross/concomitant sensitization to gallates mix and other cosmetics ingredients acting as haptens in cosmeticians and cosmetology students in occupational and non-occupational exposures. To our knowledge, no similar studies had been performed.

## Materials and methods

A descriptive cross-sectional study was conducted after obtaining approval from the Medical Ethics Board at Medical University – Sofia and in accordance with the Helsinki Declaration. A total of 109 participants (8 men and 101 women) were included in the study. The presented study is part of the scientific project “Evaluation of the prevalence of contact sensitization to ingredients of cosmetic products and health risk management” granted by the Medical University of Sofia, Contract No D-169/14.06.2022 which included 20 haptens, classified in 3 main groups: preservatives (formaldehyde, quaternium-15, DMDM hydantoin, imidazolidinyl urea, methylisothiazolinone and methylchloroisothiazolinone, iodopropynyl butylcarbamate, methylidibromoglutaronitrile, polyaminopropyl biguanide, paraben mix); fragrance markers (fragrance mix – I, peru balsam, colophonium, hydroxy-isohexyl 3-cyclohexene carboxaldehyde (HICC); surfactants/emulsifiers/emollients (cetaryl glucoside, decyl glucoside, cocamidopropyl betaine), as well as lanolin alcohol, para-phenylenediamine (PPD) and 2-hydroxyethyl methacrylate.

The participants were divided in 3 groups – 37 cosmetology students from the Medical College – Medical University – Sofia (limited exposure duration expected), 26 occupationally exposed cosmeticians (minimum 2-year occupational exposure), and 46 individuals without occupational exposure to cosmetics who served as control group. The demographic characteristics of the groups are presented in Table 1.

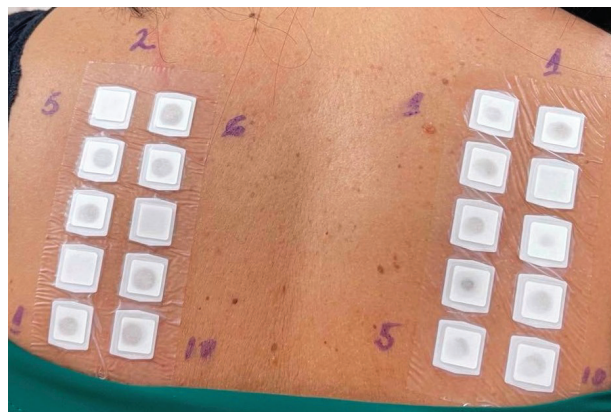
**Table 1.** Demographic characteristics of the population studied.

Group	N	Age, years		
		[Mean ± SD]	Min	Max
Cosmetology students	37	23.70 ± 6.62	18	41
Occupationally exposed cosmeticians	26	32.77 ± 9.60	20	51
Controls	46	31.98 ± 14.54	17	62
<b>Total</b>	<b>109</b>	<b>29.48 ± 11.84</b>	<b>17</b>	<b>62</b>

All the participants were informed about the purpose of the study and gave their written prior informed consent.

All the participants were skin patch tested according to the classical Jadassohn–Bloch technique with Gallate mix 1.0% pet (containing propyl gallate, dodecyl gallate and octyl gallate) - Chemotechnique Diagnostics, by placing the hapten in IQ Ultimate hypoallergenic patches of Chemotechnique Diagnostics (IQ Chambers, Vellinge,

Sweden). Lack of anti-allergic medication treatment one week before and during the testing was a mandatory requirement. Patches were applied on the upper back of the tested individuals and left for 48 hours (Fig. 1).



**Figure 1.** Patch testing technique.

Patch test reading was performed on day (D)3 or D4 and on D7. The reactions were interpreted as negative, doubtful, weakly positive (+), strongly positive (++), extremely positive (+++), and irritant reactions, as recommended by the International Contact Dermatitis Research Group (ICDRG). For the statistical analyses, reactions with least one plus (+) on D3/4 or D7 were counted as positive reactions, whereas negative, doubtful, and irritant reactions were concluded as negative.

Statistical analyzes were performed using the statistical software SPSS for Windows version 20.0. Continuous variables were presented as mean ± standard deviation (SD). The category variables were presented as a percentage. The relationship between preservatives and groups was evaluated by Fisher's exact test. A two-tailed p value < 0.05 was considered statistically significant.

## Results

Regarding the age characteristics of the tested groups (Table 1), the mean age of the students was significantly lower when compared to the control group – 23.70 ± 6.62 y compared to 31.98 ± 14.54 y (p = 0.006) and to the occupationally exposed cosmeticians – 32.77 ± 9.60 y (p = 0.008). No significant differences between the control group and the cosmeticians were observed (p = 0.957).

Data on the prevalence of sensitization to Gallate mix in the defined groups are presented in Table 2.

The results demonstrate that the prevalence of positive skin patch tests to Gallate mix among the whole tested population was high (33.9%). The positivity rate among the group of students is higher, when compared to the group of occupationally exposed cosmeticians and especially to the control group; however no significant difference between the studied groups was observed. The results indicate that despite the expected time and roots of exposure, the rate of positive reactions to the gallates mix is approximately one third (33%) of the tested participants.

**Table 2.** Prevalence of sensitization to Gallate mix in the defined groups.

Gallate mix		Controls	Students	Occupationally exposed cosmeticians	Total	p
Negative	N	36	20	16	72	0.059
	%	78.3%	54.1%	61.5%	66.1%	
Positive	N	10	17	10	37	33.9%
	%	21.7%	45.9%	38.5%	33.9%	
Total	N	46	37	26	109	

**Table 3.** Prevalence of cross/concomitant sensitization to Gallate mix and the other tested haptens in the defined groups.

Haptens	Reactions to Gallate mix						Total
	Target group						
	Control group		Students		Occupationally exposed cosmeticians		
	Negative N (%)	Positive N (%)	Negative N (%)	Positive N (%)	Negative N (%)	Positive N (%)	
PPD	3 (8.3)	0 (0)	1 (5.0)	0 (0)	1 (6.3)	0 (0)	0
2-Hydroxyethyl methacrylate	4 (11.1)	3 (30.0)	1 (5.0)	1 (5.9)	5 (31.3)	0 (0)	4
Colophonium	1 (2.8)	2 (20.0)	1 (5.0)	4 (23.5)	1 (6.3)	0 (0)	6
Peru balsam	3 (8.3)	2 (20.0)	3 (15.0)	3 (17.6)	3 (18.8)	1 (10.0)	6
Paraben mix	1 (2.8)	0 (0)	2 (10.0)	0 (0)	2 (12.5)	0 (0)	0
Fragrance mix – I	3 (8.3)	2 (20.0)	1 (5.0)	0 (0)	4 (25.0)	4 (40.0)	6
Cocamidopropyl betaine	4 (11.1)	3 (30.0)	0 (0)	1 (5.9)	3 (18.8)	1 (10.0)	5
Lanolin	5 (13.9)	3 (30.0)	2 (10.0)	0 (0)	6 (37.5)	2 (20.0)	5
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	4 (11.1)	2 (20.0)	1 (5.0)	3 (17.6)	4 (25.0)	2 (20.0)	7
Decyl glucoside	0 (0)	3 (30.0)	6 (30.0)	4 (23.5)	3 (18.8)	0 (0)	7
	<b>*p = 0.008</b>						
Quaternium-15	2 (5.6)	1 (10.0)	3 (15.0)	2 (11.8)	2 (12.5)	0 (0)	3
Formaldehyde	2 (5.6)	0 (0)	3 (15.0)	7 (41.2)	6 (37.5)	2 (20.0)	9
DMDM hydantoin	2 (5.6)	1 (10.0)	4 (20.0)	2 (11.8)	2 (12.5)	1 (10.0)	4
Imidazolidinyl urea	2 (5.6)	1 (10.0)	0 (0)	1 (5.9)	1 (6.3)	2 (20.0)	4
Methylisothiazolinone + Methylchloro-isothiazolinone	3 (8.3)	1 (10.0)	2 (10.0)	1 (5.9)	2 (12.5)	1 (10.0)	3
Iodopropynyl butylcarbamate	1 (2.8)	1 (10.0)	1 (5.0)	1 (5.9)	0 (0)	1 (10.0)	2
Methyldibromo-glutaronitrile	3 (8.3)	1 (10.0)	2 (10.0)	1 (5.9)	2 (12.5)	1 (10.0)	3
Polyaminopropyl biguanide	4 (11.1)	1 (10.0)	3 (15.0)	1 (5.9)	0 (0)	0 (0)	2
Cetearyl glucoside	3 (8.3)	3 (30.0)	2 (10.0)	4 (23.5)	1 (6.3)	0 (0)	7

A significantly higher ( $p = 0.008$ ) prevalence of co-sensitization to Decyl glucoside was established for the control group.

The results on the cross/concomitant sensitization to gallate mix and other haptens included in the patch testing are summarized below – Table 3.

## Discussion

In principle, skin sensitization is no different to other toxicological hazards and is considered as an immunotoxicological adverse health effect. It represents an enhanced risk of developing allergic contact dermatitis and is included as an endpoint in general toxicological testing and risk assessment of chemicals (Bou Zerdan et al. 2021).

It should be noted that a positive patch test reaction does not automatically indicate a clinical problem. Gallates sensitization can have a variety of clinical manifestations, usually cheilitis and dermatitis of the hands (Holcomb et al. 2017). The most common sensitizing agent in cosmetics is lipstick and lip products (Gamboni et al. 2013) and in occupational environment, bakery products (octyl gallate) and in lower extend cheese sellers (García-Melgares et al. 2007). For rosacea patients, the most common allergens giving positive results were octyl

gallate (10.68%) and dodecyl gallate (8.74%) (Ozbagcivan et al. 2020).

Our results on the prevalence of contact sensitization to the selected ingredients focused our attention to gallates, since such high prevalence was not observed for any of the other substances, tested in the present study, except for formaldehyde with 18.3% positivity rate (results presented in another study) (Lyapina et al. 2023 a, b).

In a review of 74 cases of positive reactions to gallates tests over a 40-year period, no hypersensitivity to E310 was observed after oral exposure. Propyl gallate was the most commonly reported contact allergen often inducing reactions of skin contact sensitization - facial and/or hand dermatitis (Holcomb et al. 2017). There is also a possibility of coexistence of hypersensitivity not only between PG and octyl gallate, but with other haptens as well. Our findings on the significantly higher prevalence of co-sensitization to Gallate mix and decyl glucoside need further examination, taking into consideration the limitations of cross-sectional studies. We should also point out that no similar studies and results were found in the available scientific literature and further studies are required in this field.



Studies indicate that the prevalence of allergic contact dermatitis to propyl gallate is increasing concomitantly with the reduced use of this antioxidant by the food industry. Among patch tested patients during the period 1988–2005, a statistically significant increase in propyl gallate positivity rates has been observed over the last decade, which could be attributable to the increased use of propyl gallate in the cosmetics. However, the authors suggest that the concomitant reduction of use of propyl gallate in food, with oral tolerance being less likely to develop, may also be a contributing factor for the increasing trend of propyl gallate allergic contact dermatitis (Perez et al. 2008).

Our results seem to support the latter statement, since the highest sensitization rates were observed in the group of students. The role of more intensive exposure to cosmetics cannot be excluded as well, as evidenced by the high prevalence of sensitization among the group of cosmeticians. Usually, females exhibit more vigorous humoral responses and cell mediated immune responses to antigenic stimulation than males (Ruggieri et al. 2016). Bearing in mind the gender characteristics of the cosmetician occupation, with high predominance of females, we could consider higher risk of subclinical contact sensitization due to more frequent exposures to allergens.

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## Conclusion

This pilot study established a high prevalence of contact sensitization to gallates, the group of students and occupationally exposed cosmeticians being at higher risk. We could speculate the role of the reduced use of propyl gallate in food as a contributing factor, with oral tolerance being less likely to develop, as well as the repetitive use of cosmetics. Nevertheless, basing on the limitations of the study being a pilot and cross-sectional one, with a relative small number of tested individuals, we could point out the need for further investigations to validate the reliability of the present findings. Proper risk information, health education, development and dissemination of practical tools for workplace risk assessment and management as well as the introduction of systematic programs for prevention of occupational skin diseases should be recommended.

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