Amended Safety Assessment of Alkyl Gallates as Used in Cosmetics

Status:	Draft Final Amended Report for Panel Review
Release Date:	September 11, 2026
Panel Meeting Date:	October 5 – 6, 2026

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Bruce A. Brod, M.D., M.H.C.I., F.A.A.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. Previous Panel member involved in this assessment: David E. Cohen, M.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., Associate Toxicologist/Senior Scientific Analyst/Writer, CIR.

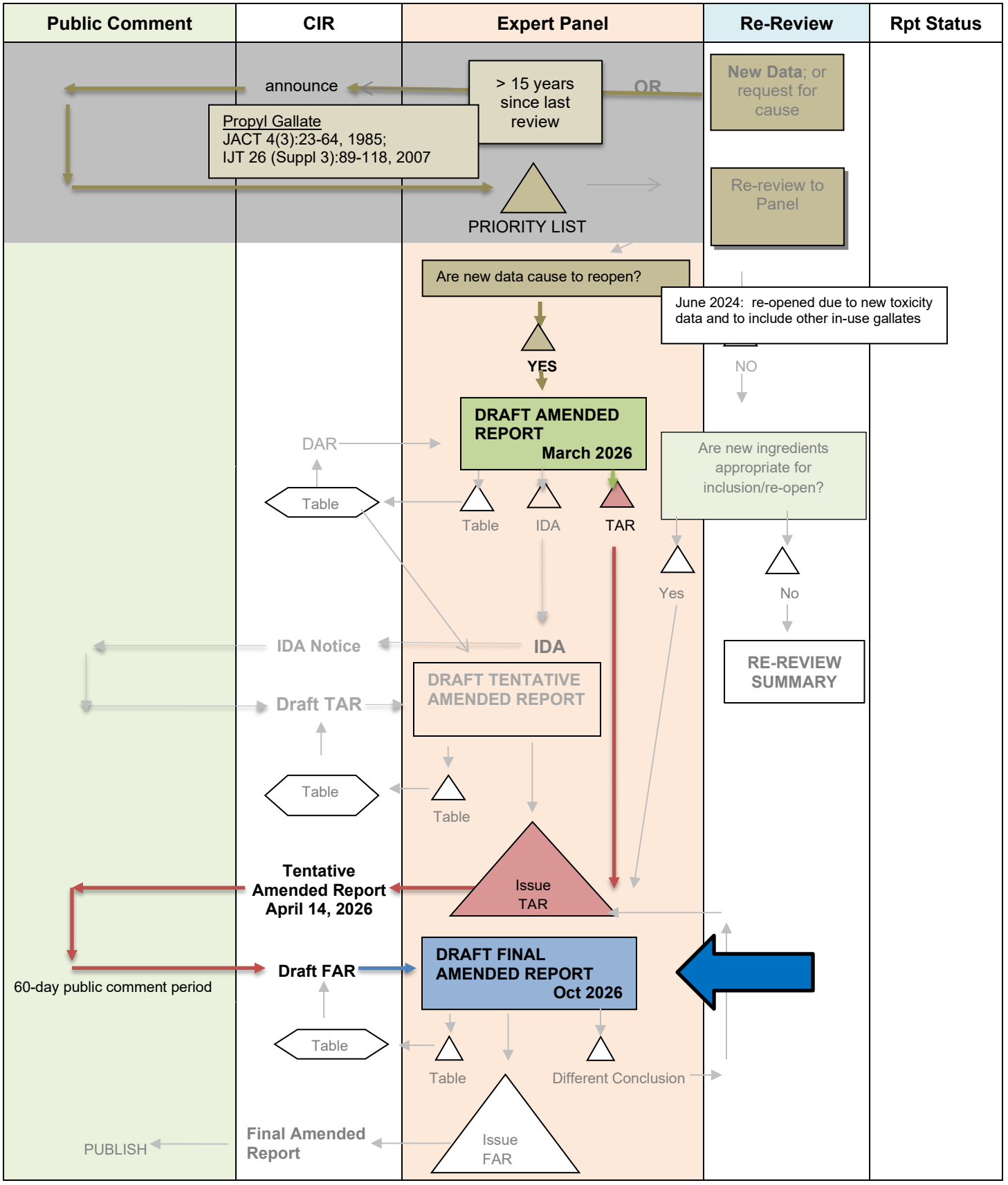
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RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Alkyl Gallates

MEETING October 2026



Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Priya Ferguson, M.S.
Associate Toxicologist/Senior Scientific Analyst/Writer, CIR

Date: September 11, 2026

Subject**:** Amended Safety Assessment of Alkyl Gallates as Used in Cosmetics

Enclosed is the Draft Final Amended Report of the Safety Assessment of Alkyl Gallates as Used in Cosmetics (*report_AlkylGallates_102026*). At the March 2026 meeting, the Panel issued a Tentative Amended Report with the conclusion that the 4 alkyl gallates are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating and non-sensitizing.

Since the March 2026 meeting, no new data have been received; however, a recently published retrospective patch test study (series included Caprylyl Gallate and Dodecyl Gallate) performed in atopic patients was found. This study has been incorporated into the report in highlighted text.

Comments received from the Council on the March Draft Report and on the Tentative Report have been received, and addressed (*PCPCcomments1_AlkylGallates_102026*; *PCPCcomments2_ AlkylGallates_102026* and *response-PCPCcomments1_ AlkylGallates_102026*; *response-PCPCcomments2_AlkylGallates_102026).* Other documents included in this packet include the following:

- flow chart (*flow_AlkylGallates_102026*)
- report history (*history_AlkylGallates_102026*)
- search strategy (*search_AlkylGallates_102026*)
- data profile (*dataprofile_AlkylGallates_102026*)
- original 1985 report on Propyl Gallate (*originalreport1985_AlkylGallates_102026*)
- 2007 amended report on Propyl Gallate (*amendedreport2007_AlkylGallate_102026*)
- minutes from the meetings at which the original reports were discussed (*originalminutes_AlkylGallates_102026*)
- transcripts from recent meetings (*transcripts_AlkylGallates_102026*)

The Panel should carefully review the Abstract, Discussion, and Conclusion, and issue a Final Amended Report.

History – Alkyl Gallates

1985

- publishing of Final Report on Propyl Gallate with the following conclusion: “Propyl Gallate is safe as a cosmetic ingredient at concentrations not exceeding 1%:

2007

- published of Final Amended Report on Propyl Gallate with the following conclusion: “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%”

June 2024

- Panel evaluates re-review of Propyl Gallate and determines to re-open safety assessment due to new toxicity data and inclusion of in-use gallates (Caprylyl Gallate, Dodecyl Gallate, and Ethylhexyl Gallate)

December 2024

- concentration of use data received

February 2026

- updated concentration of use received

March 2026

- comments on Draft Amended Report received from Council
- Panel reviews Draft Amended Report on the 4 alkyl gallates and issued Tentative Report with conclusion that these ingredients are safe when formulated to be non-irritating and non-sensitizing

April 2026

- comments on Tentative Report received from Council

October 2026

- Panel reviews Draft Final Amended Report

Alkyl Gallates Data Profile* – October 2026 – Writer, Priya Ferguson

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Caprylyl Gallate	**X**			X	X	X					X				X								XO	X				X
Dodecyl Gallate	**X**		X	X		X					X												XO	X				X
Ethylhexyl Gallate	**X**																												
Propyl Gallate	**XO**	**O**	XO	X		XO	X	X O		O	X O			XO	XO	XO		O	X	O	O		XO	XO	O	XO	O	X	X

* "X" indicates that data were available in a category for the ingredient; "O" indicates that data were available in the 2007 amended report on Propyl Gallate

Alkyl Gallates

Ingredient	CAS #	PubMed	FDA	CompTox	ChemPort	NIOSH	NTIS	NTP	FEMA	EU	ECHA	SIDS	SCCS	AICIS	FAO	WHO	Web
Propyl Gallate	121-79-9	x	x	x	x		x	x	x		x				x		
Caprylyl Gallate	1034-01-1	x	x	x	x												
Dodecyl Gallate	1166-52-5	x	x	x	x										x		
Ethylhexyl Gallate	34531-26-5				x												

x = studies found

Search Strategy

-ingredients were searched as INCI names along with qualifiers listed below in PubMed:
-CAS numbers also searched
-Octyl Gallate and Lauryl Gallate also searched as they are synonymous to Caprylyl and Dodecyl Gallate, respectively
-qualifiers:

- -allergy
- -toxicity
- -dermal
- -cosmetic
- -manufacturing
- -ocular
- -irritation
- -sensitization
- -penetration
- -absorption
- -metabolism
- -safety

Personal Care Products Council

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Jaap Venema, Ph.D.
EVP and Chief Scientist – Personal Care Products Council
Industry Liaison to the CIR Expert Panel

DATE: March 6, 2026

SUBJECT: Draft Amended Report: Safety Assessment of Alkyl Gallates as Used in Cosmetics (March 2026 meeting draft)

The Personal Care Products Council respectfully submits the following comments on the draft amended report, Safety Assessment of Alkyl Gallates as Used in Cosmetics.

Key Issue

Introduction – The Introduction should also note that the Dictionary lists Octyl Gallate as a former INCI name for Ethylhexyl Gallate. For recent papers, it is appropriate to assume that octyl gallate represents Caprylyl Gallate. Unfortunately, in the past, octyl was frequently used for ethylhexyl, so the assumption that octyl gallate represents the straight chain may not always be correct in older papers.

Additional Considerations

Abbreviations – Please correct the definition for T1/2 (it should be half-life, or time to degrade by 50%) and Tmax1 (it currently says “time to reach Cmax2”).

Impurities, old report summary – It is not clear what these specifications represent. Are they Food Chemical Codex specifications? Have they changed since the original report was published? Is it necessary to include old specifications in a new CIR report as only the current specifications are relevant?

Impurities, Propyl Gallate – The reference to Dodecyl Gallate should be removed from the subsection on Propyl Gallate.

Cosmetic Use – Rather than saying "Some of these ingredients may result in incidental ingestion" and "Some of these ingredients are also used near the eye", please be more specific. Only Propyl Gallate and Ethylhexyl Gallate are used in lip and eye area products.

Non-Cosmetic Use, old report summary – Please revise: "Propyl Gallate may also be used as a pressure-sensitive adhesive." It may be used "in" pressure-sensitive adhesives, it is not an adhesive.

Toxicokinetics; Summary – As the in vitro dermal penetration study is a key study for assessing exposure to Caprylyl Gallate, it would be helpful to include more details in the text. The text is not clear as to what the 14% percutaneous absorption represents. The text should indicate that this is the amount that was recovered in the skin (epidermis and dermis) and receptor fluid. Only 1.5% was recovered in the receptor fluid.

Toxicokinetics – The oral study in rats should indicate in which media (plasma) the half-lives were determined.

Repeated-Dose, old report summary – The summary appears to have two sentences about the same study. "Rats fed 0.035-0.5% Propyl Gallate for 3 mo and pigs fed 0.2% Propyl Gallate showed no treatment related effects." and "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." The first sentence with fewer details should be deleted.

Developmental and Reproductive Toxicity – It should be noted that the multigeneration study cited to the ECHA dossier (reference 4) was attributed to a 1955 study by Van Esch that was also cited in the original CIR report.

Developmental and Reproductive Toxicity; Summary - Please correct: "associated with various functions in the testis when evaluated given to mice via intraperitoneal injection for 4 wk"

Genotoxicity, old report summary – If available, the concentrations/doses used in the hamster lung chromosomal aberration assay should be stated.

Anti-Carcinogenicity, Dodecyl Gallate – At what doses was the regression and prevention of tumors statistically significantly increased compared to rats not treated with Dodecyl Gallate?

Effect on Enzymes, old report summary – What concentrations/doses were used in the studies described in this section?

Inhibition of Developmental and Reproductive Toxicity – This section should be presented directly after the Developmental and Reproductive Toxicity section.

Effect of Carbon Chain Length on Hydrolysis and Transport Characteristics of Alkyl Gallates; Summary – The information in this section should be moved to the ADME section. The composition of the "mucosal solution" should be stated.

Phototoxicity/Photosensitization – The following is not a complete sentence: “Similarly, no photosensitization in an assay performed in 25 subjects using 10% Propyl Gallate in alcohol.”

Summary – The first sentence states that 3 alkyl gallates are included in this report – this needs to be corrected as there are 4 alkyl gallates included in this report.

Please revise: “for the addition for the evaluation of new data and for the addition of structurally similar ingredients”

Table 3 – Please revise Table 3 to be consistent with the memo from PCPC concerning tattoo preparations (memo dated February 26, 2026).

Table 4 – The identity of the receptor fluid should be included in the description of the in vitro study completed in porcine skin.

Alkyl Gallates – October 2026 – Priya Ferguson	
Comment Submitter: Personal Care Products Council **Date of Submission: March 6, 2026**	
Comment	**Response/Action**
Introduction – The Introduction should also note that the Dictionary lists Octyl Gallate as a former INCI name for Ethylhexyl Gallate. For recent papers, it is appropriate to assume that octyl gallate represents Caprylyl Gallate. Unfortunately, in the past, octyl was frequently used for ethylhexyl, so the assumption that octyl gallate represents the straight chain may not always be correct in older papers.	Addressed
Abbreviations – Please correct the definition for T1/2 (it should be half-life, or time to degrade by 50%) and Tmax1 (it currently says "time to reach Cmax2").	Addressed
Impurities, old report summary – It is not clear what these specifications represent. Are they Food Chemical Codex specifications? Have they changed since the original report was published? Is it necessary to include old specifications in a new CIR report as only the current specifications are relevant?	Addressed
Impurities, Propyl Gallate – The reference to Dodecyl Gallate should be removed from the subsection on Propyl Gallate	Addressed
Cosmetic Use – Rather than saying "Some of these ingredients may result in incidental ingestion" and "Some of these ingredients are also used near the eye", please be more specific. Only Propyl Gallate and Ethylhexyl Gallate are used in lip and eye area products.	Language kept as it is consistent across CIR reports
Non-Cosmetic Use, old report summary – Please revise: "Propyl Gallate may also be used as a pressure-sensitive adhesive." It may be used "in" pressure-sensitive adhesives, it is not an adhesive.	Addressed
Toxicokinetics; Summary – As the in vitro dermal penetration study is a key study for assessing exposure to Caprylyl Gallate, it would be helpful to include more details in the text. The text is not clear as to what the 14% percutaneous absorption represents. The text should indicate that this is the amount that was recovered in the skin (epidermis and dermis) and receptor fluid. Only 1.5% was recovered in the receptor fluid.	Addressed
Toxicokinetics – The oral study in rats should indicate in which media (plasma) the half-lives were determined.	Addressed
Repeated-Dose, old report summary – The summary appears to have two sentences about the same study. "Rats fed 0.035-0.5% Propyl Gallate for 3 mo and pigs fed 0.2% Propyl Gallate showed no treatment related effects." and "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	Addressed

histopathological parameters." The first sentence with fewer details should be deleted.	
Developmental and Reproductive Toxicity – It should be noted that the multigeneration study cited to the ECHA dossier (reference 4) was attributed to a 1955 study by Van Esch that was also cited in the original CIR report.	Addressed
Developmental and Reproductive Toxicity; Summary - Please correct: "associated with various functions in the testis when evaluated given to mice via intraperitoneal injection for 4 wk"	Addressed
Genotoxicity, old report summary – If available, the concentrations/doses used in the hamster lung chromosomal aberration assay should be stated.	Addressed
Anti-Carcinogenicity, Dodecyl Gallate – At what doses was the regression and prevention of tumors statistically significantly increased compared to rats not treated with Dodecyl Gallate?	Addressed
Effect on Enzymes, old report summary – What concentrations/doses were used in the studies described in this section?	Addressed
Inhibition of Developmental and Reproductive Toxicity – This section should be presented directly after the Developmental and Reproductive Toxicity section.	Kept as is
Effect of Carbon Chain Length on Hydrolysis and Transport Characteristics of Alkyl Gallates; Summary – The information in this section should be moved to the ADME section. The composition of the "mucosal solution" should be stated.	Addressed
Phototoxicity/Photosensitization – The following is not a complete sentence: "Similarly, no photosensitization in an assay performed in 25 subjects using 10% Propyl Gallate in alcohol."	Addressed
Summary – The first sentence states that 3 alkyl gallates are included in this report – this needs to be corrected as there are 4 alkyl gallates included in this report.	Addressed
Please revise: "for the addition for the evaluation of new data and for the addition of structurally similar ingredients"	Addressed
Table 3 – Please revise Table 3 to be consistent with the memo from PCPC concerning tattoo preparations (memo dated February 26, 2026).	Addressed
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Personal Care Products Council

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Jaap Venema, Ph.D.
EVP and Chief Scientist – Personal Care Products Council
Industry Liaison to the CIR Expert Panel

DATE: April 30, 2026

SUBJECT: Tentative Amended Report: Amended Safety Assessment of Alkyl Gallates as Used in Cosmetics (release date April 14, 2026)

The Personal Care Products Council respectfully submits the following comments on the draft amended report, Safety Assessment of Alkyl Gallates as Used in Cosmetics.

Key Issues

Discussion – As the conclusion includes the qualification of "when formulated to be non-irritating and non-sensitizing", it would be helpful if the Discussion described why the Expert Panel included these qualifications.

Conclusion – As three of these ingredients have no use concentrations reported, it would be helpful to include the footnote that the ingredients without use concentrations should be used in product categories and at concentrations like that reported for Propyl Gallate.

Additional Considerations

Chemical Properties – Presenting molecular weights and octanol-water partition coefficients as ranges without associating the values with specific ingredients is not helpful. Please state the molecular weight and partition coefficient of Propyl Gallate with its name, and the values for Dodecyl Gallate.

Reactivity, old report summary – Please correct: "stable in in neutral…" (delete second "in")

Non-Cosmetic Use – It would be helpful to note that FDA requires that Propyl Gallate used in food conform to the specification included in the *Food Chemical Codex*.

Toxicokinetics; Summary – When describing the PBK model, it should be made clear that they are modeling the oral route of exposure.

Repeated-Dose, old report summary – The following two sentences are describing the same study. Please delete one of these sentences. "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."

Developmental and Reproductive Toxicity; Table 6 – In the description of the Zebrafish study, it should say that microinjection was used to inject Propyl Gallate into the yolk sacs of the embryos (rather than being injected directly into the embryos as suggested by the CIR report).

Anti-Carcinogenicity, Caprylyl Gallate – Please correct the following sentence: "The cellular morphology of breast cancer tissues administered with Caprylyl Gallate showed almost normal tissue structure with minor or no remarkable changes." Please make it clear that rats were treated with Caprylyl Gallate, not the breast cancer tissues.

Mutagenesis Enhancement, old report summary – Please include the concentration (or dose) of Propyl Gallate that "induced a 700% increase in mutagenic frequency of 4-NQO in TA98."

Effect on Hepatotoxicity, old report summary – Please delete "it" from the following: "In vitro, Propyl Gallate at 0.5 – 2.0 mM it caused dose-dependent rat hepatocyte toxicity."

Inhibition of Developmental and Reproductive Toxicity, old report summary – Please move this section after the Developmental and Reproductive Toxicity section (similar to the Anti-Carcinogenicity Studies being presented after the Carcinogenicity Studies).

Renal Toxicity – Please revise the following sentence: "Renal toxicity, characterized by tubular degermation and regeneration, increased urinary neutrophil gelatinase-associated lipocalin, and produced occasional increases in serum creatinine and urea nitrogen." (based on the structure of the sentence, it is saying that renal toxicity produced the increases in serum creatinine and urea nitrogen)

Estrogenic Effects – The following sentence would be clearer if "for Propyl Gallate" was added as indicated in brackets. "[For Propyl Gallate], 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 x 10-7 μM and 6.6 x 10-6 μM for estradiol, respectively."

Dermal Irritation and Sensitization (last paragraph); Table 8; Table 9 – For many of the patch test studies, the vehicle is incorrectly listed as "petroleum". It should be "petrolatum" (often abbreviated as pet.).

Occupational Exposure Study – Please correct: "patch rest reactions" ("rest" should be "test")

Summary – Please revise the following sentence: “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.”

Table 4, reference 26 – Since only one dose was used, it would be clearer to state “(1/sampling time)” compared to “(1/group)”, in the test system column.

Table 5, reference 4 (last row) – If available, please also state the mg/kg bw doses for all the dietary concentrations used (not just for the NOAEL).

Table 7, reference 44 (last row) – To be consistent with the rest of the table, the Concentration/Dose column should be “0, 2000 mg/kg bw” to indicate that the study included a control group.

Table 8, Animal (last row) – To be consistent with the results from the LLNA on Dodecyl Gallate, please state the SI values (or EC3 value) for the LLNA on Propyl Gallate if they are available.

Table 9 – Is it necessary to divide human patch test studies into “retrospective” and “prospective”?

In the Methods/Details column of the Propyl Gallate row for reference 67 it says: “patch testing using 1% Dodecyl Gallate”. “Dodecyl Gallate” should be “Propyl Gallate”.

Alkyl Gallates – October 2026 – Priya Ferguson	
Comment Submitter: Personal Care Products Council **Date of Submission: April 30, 2026**	
Comment	**Response/Action**
Discussion – As the conclusion includes the qualification of "when formulated to be non-irritating and non-sensitizing", it would be helpful if the Discussion described why the Expert Panel included these qualifications	Addressed
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Chemical Properties – Presenting molecular weights and octanol-water partition coefficients as ranges without associating the values with specific ingredients is not helpful. Please state the molecular weight and partition coefficient of Propyl Gallate with its name, and the values for Dodecyl Gallate	values with associated ingredients may be found in Table 2
Reactivity, old report summary – Please correct: "stable in in neutral…" (delete second "in")	Addressed
Non-Cosmetic Use – It would be helpful to note that FDA requires that Propyl Gallate used in food conform to the specification included in the Food Chemical Codex.	Not included as not likely relevant to cosmetic specifications.
Toxicokinetics; Summary – When describing the PBK model, it should be made clear that they are modeling the oral route of exposure.	Addressed
Repeated-Dose, old report summary – The following two sentences are describing the same study. Please delete one of these sentences. "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."	Addressed
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Mutagenesis Enhancement, old report summary – Please include the concentration (or dose) of Propyl Gallate that "induced a 700% increase in mutagenic frequency of 4-NQO in TA98."	Concentration not stated in report.
Effect on Hepatotoxicity, old report summary – Please delete "it" from the following: "In vitro,	Addressed

Propyl Gallate at 0.5 – 2.0 mM it caused dose-dependent rat hepatocyte toxicity."	
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Summary – Please revise the following sentence: "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."	Addressed
Table 4, reference 26 – Since only one dose was used, it would be clearer to state "(1/sampling time)" compared to "(1/group)", in the test system column.	Addressed
Table 5, reference 4 (last row) – If available, please also state the mg/kg bw doses for all the dietary concentrations used (not just for the NOAEL)	Not available
Table 7, reference 44 (last row) – To be consistent with the rest of the table, the Concentration/Dose column should be "0, 2000 mg/kg bw" to indicate that the study included a control group.	Addressed
Table 8, Animal (last row) – To be consistent with the results from the LLNA on Dodecyl Gallate, please state the SI values (or EC3 value) for the LLNA on Propyl Gallate if they are available.	Not available
Table 9 – Is it necessary to divide human patch test studies into "retrospective" and "prospective"?	Table left as is
In the Methods/Details column of the Propyl Gallate row for reference 67 it says: "patch testing	Addressed

using 1% Dodecyl Gallate". "Dodecyl Gallate" should be "Propyl Gallate"	

JUNE 2024 MEETING – RE-REVIEW STAGE

Belsito Team – June 3, 2024

DR. BELSITO: Then we're going to move to propyl gallate. Again, this is a re-review. Okay. Okay. So, the Expert Panel first published a review of safety of propyl gallate in 1985. The Panel concluded on the basis of the available information presented in the report that propyl gallate was safe as a cosmetic ingredient at concentrations not exceeding one percent. Panel reopened the report in 2003 to consider sensitization potential of propyl gallate at lower concentrations than originally thought. Based on the data evaluated at the re-review process, we concluded that propyl gallate is safe in the present practice of use described in the safety assessment at concentrations less than one percent and published that in 2007 as a final report.

Because it's been 15 years since the previous report has been issued, we're looking at the data again. There are newly found studies, including updated regulatory limits for human and animal consumption, in vitro genotox, in vitro developmental and repro tox, studies on estrogenic effects, in vitro effects on tumor cells, in vitro dermal irritation studies, ocular irritation, patch test reports. We have data on an in vitro developmental and repro tox, developmental toxicity in zebrafish that were not present in the original report. And we have a table of current hysterical -- historical, not hysterical, uses. According to the 2023 VCRP, propyl gallate has 86 reported uses, down from 164 in 2002. Maximum reported concentration of use, 0.12 percent in eyeliners compared to 0.1 in other personnel cleanliness products, as reported in 2003 -- 0.012, excuse me.

So, looking at these new studies, the question is, do we want to reopen? My first question is, why are we not including a whole list of other gallates that are included in the dictionary, which is why I wanted to get into the INCI Dictionary? There are a lot of them. There's capryl gallates, citronella gallate, dodecyl gallate, glucosyl gallate, maleic gallate, propyl gallates, stearyl gallate. The ones that I see coming up on labels in particular and that we patch test for are dodecyl gallate, propyl gallate, obviously, and stearyl gallate. So, there're a whole bunch of other ingredients we can bring in here that wasn't mentioned.

DR. HELDRETH: We can go down that pathway and look for those that are used and consider reopening it to add. But within the last couple years, we kind of changed course on trying to do large numbers of ingredient and focus on smaller projects. But we're happy to search those out and suggest a group of ingredients to add if that's the Panel's purview -- or Panel's --

DR. RETTIE: Would be interesting to know if these other gallates are used in the same way as propyl gallate. I don't know that.

DR. BELSITO: They are. They're all antioxidants.

DR. RETTIE: They're all the same. I would say that was an argument maybe for bringing them in.

DR. BELSITO: Well, the three I deal with are antioxidants, and they're included on a cosmetic panel. I believe they're used in foods, as well as, as you may have read, they're used in margarine, peanut butter. They're sort of antioxidants in oily products, and it's pretty much the way they're used in cosmetics as well. But we don't have to do this. I did this because I test with two other gallates, and I suddenly wondered why we weren't doing it. And then I went to the cosmetic ingredient -- or the INCI Dictionary, and I saw that there were a whole list of gallates that I wasn't even aware of that are listed in that dictionary. And I thought we were still working under the assumption that we wanted to clear as many ingredients in the dictionary as possible. But if we don't and we don't think the new data warrants reopening, I'm fine with that too. So, I'll just pass that out to you for discussion.

DR. HELDRETH: Yeah, looking at the other gallates that are in the dictionary and cross-referencing it with the 2023 VCRP data that we are have, the next highest gallate after propyl gallate with a simple alkyl chain on it that's in use is only used in five products.

DR. BELSITO: What's that?

DR. HELDRETH: Dodecyl gallate.

DR. BELSITO: Dodecyl.

DR. HELDRETH: In fact, according to VCRP data, there's only three gallates reported in use in 2023. There's the propyl gallate, and then there's a not-simple alkyl gallate. It's this epigallocatechin gallate, but I don't think that that is anywhere near the same as the simple alkyl gallates here. And dodecyl is the only other one with reported use. So, there's really just one other reported ingredient and use that's a simple alkyl gallate, and it's only five uses.

DR. BELSITO: Okay. Paul, what did you make of the DART studies, the new DART studies?

DR. SNYDER: I didn't have any issues with them, not at that low -- that 0.01 percent. So, I didn't have any issues with them.

DR. RETTIE: Paul, did you look at the zebrafish data showing pericardial toxicity at the way low 50 ppm?

DR. SNYDER: Yeah, I'm not familiar with zebrafish data, to be honest with you, in that repro world. So, that's not my area.

DR. KLAASSEN: Yeah, I read that with some interest and with not a lot of knowledge either, and I was hoping that Susan might be able to increase our knowledge in this area. There are people at her institution that use this zebrafish a lot.

DR. BELSITO: They're considered a really good embryo model for -- zebrafish are considered a real good model for human reproductive toxicity and had been used as a workaround for the EU ban on cosmetic use of animals since they were embryo, but now I think EU is changing. I heard that recently in Scotland that EU's not going to allow zebrafish either soon or currently do not. But they used to. So, they were being used in cosmetics to look at DART, and they were considered a good model for human DART.

DR. RETTIE: This is not necessarily DART that we're looking at here. Pericardial tox is different. The group's seemed happy to accept zebrafish as one of the newer models, as you noted, for DART or endogenic toxicity, and that's all good. But more general sort of tissue toxicities, I wasn't clear on that.

DR. BELSITO: For tissue.

DR. KLAASSEN: This is, I think, a developmental study, wasn't it?

DR. BELSITO: Yeah.

DR. RETTIE: It is? Okay. Then I withdraw those comments.

DR. KLAASSEN: Okay.

DR. BELSITO: On PDF Page 6 under Carcinogenicity Studies, the second one, the Park study, the human pulmonary fibroblast cell line, that's not a carcinogenicity study, is it? It's looking at cell cycle and human pulmonary fibroblast. I mean --

MS. RAJ: Well, I think because we typically put studies that are looking at transformation or any change in cancer cell lines under in vitro cell transformation.

DR. BELSITO: It doesn't say that it's a cancer cell line. It says, "Human pulmonary fibroblast cells."

MS. RAJ: I can move that. I guess, what would be the more appropriate (inaudible) put that under?

DR. BELSITO: The one above it is on a cancer cell line. But the two below it are on human pulmonary fibroblast. Both those two lower Park studies don't seem to belong under Carcinogenicity. I think it has to do with one is down regulating superoxide dismutase, and the other is looking at cell cycle growth. Paul, where would you put studies like that?

DR. SNYDER: I'm not quite certain.

DR. BELSITO: Yeah.

DR. KLAASSEN: There is a section here -- I don't know if it belongs -- but Effects on Enzymes and Enzyme Systems.

DR. BELSITO: Well, the dismutase could go there. I think it would just be other effects cell growth.

MS. RAJ: Yeah.

DR. KLAASSEN: Yeah, well, there's Cellular and Tissue Effects.

DR. BELSITO: Yeah.

MS. RAJ: Okay.

DR. BELSITO: Probably go there.

DR. RETTIE: Yeah, the only other notes I had on it were the in vitro dermal study was negative. Ocular irritation that you noted was positive. And also, estrogen antagonist activity's not reported for this, which I thought was interesting.

DR. BELSITO: So, do we need to reopen it for that? Are you thinking it's interesting? Again, we need to happen to be looking at data and saying does it cause use to reopen.

DR. RETTIE: I'm looking at a no-to-maybe here, which doesn't help. I was going to be guided by the rest of your comments. It was no for me to begin with because the new tox data were at high doses, unless missed something, very high doses.

DR. BELSITO: Yeah, I was more concerned about the DART data, but Paul is not. The only other comment that I had on this report is that our two other discussions, in my estimation, were grossly deficient. The 1980 discussions always were, but I thought by 1990s we got better. We didn't discuss the ocular irritation data, the DART data, and the mutagenicity data in terms of applied dose versus what would be absorbed by the humans because it predicted lack of dermal absorption free radical scavenging. I don't know. I had question mark, reopen to include other gallates, and discuss the new DART and genotox data, and write a better discussion.

DR. RETTIE: I could go there.

DR. KLAASSEN: Fine with me.

DR. BELSITO: Paul?

DR. SNYDER: Yeah, I'm fine with that. There's a lot of teratogenesis data in the old report at very high doses given orally, so we can do that. We can reopen, and we can decide to close.

DR. BELSITO: Yeah, I saw that too, but we never put that in the discussion, why we dismissed all that teratogenic data. Reading those discussion from the two prior reports, I was just shocked at the way we put it. I mean, they're clearly not the type of discussions that we write now.

DR. SNYDER: Well, I think that's a good reason, Don, to reopen it and bring it up to date with our current language and how we discuss things. So, let's reopen it.

DR. BELSITO: And add as many of the gallates as we can, even though they're low use.

DR. HELDRETH: Yeah, there's just one other one that is in reported use, and we'll need to give Carol time because we haven't asked for a concentration of use.

DR. BELSITO: Right. But we could add all the other simple, no-brainer alkyl gallates.

DR. HELDRETH: If that's the Panel's desire, we certainly can. But I remind the Panel that the dictionary is a listing of potentially to be used chemicals and cosmetic ingredients, the vast majority of which are not in use. There's something like 35,000 entries in the dictionary, and we think maybe 6500 are in use. So, it may be a case of we're chasing after the safety of something that we have no reported use for it.

DR. BELSITO: But we've been doing that. We put an asterisk, not reported in use, but if to be used, we assume it will be used for the same cosmetic functions and the same concentrations of uses in this report.

DR. HELDRETH: And we're happy to do that.

DR. BELSITO: We've been doing it. I wasn't aware that suddenly we made a decision to shift back to just looking at the reports we were looking at.

DR. SNYDER: I think it's okay to say reopen and consider adding others. It doesn't mean we're going to. We're just going to consider. So, let's do it.

DR. BELSITO: Okay. Yeah, okay. So, we want to reopen and look at the INCI Dictionary, take in all the alkyl gallates that could reasonably be added, at least as an initial first hit on this. We can always drop some from the report if we decide we don't want to. And they can go to the Read-Across Working Group, and they can come up with a reasonable proposal. Hopefully, those can come to us so that the decision has already been made and any acceptable read-acrosses are in the documents that we're seeing, not in the Wave 2 documents. And then we don't know if they're going to be brought in or not.

DR. HELDRETH: Okay.

DR. BELSITO: Okay. Thank you.

DR. RETTIE: Thanks, Don.

DR. BELSITO: Okay. So, we're going to move on to yeast. This is Priya. Is she with --

MS. RAJ: She's probably in the other room. Could check.

DR. BELSITO: So, we got a huge Wave 2 on this. Well, it's 11:55. Are we going to get through this in five minutes? I don't think so.

DR. KLAASSEN: Let's break.

DR. BELSITO: Well, is there something we can move to? So, we're going to have yeast, prostaglandin, and amphocarboxylates, and inositol to come back to in the afternoon. Potassium cocoyl hydrolyzed collagen, why don't we do that. And if the writer's not here, you can let them know because this is a re-review.

DR. HELDRETH: Okay.

DR. BELSITO: Okay. So, let's go to that, and then we can break.

Cohen Team – June 3, 2024

DR. COHEN: Okay. Propyl gallate. Propyl gallate was first published in a review in 1985 with a conclusion of safe as a cosmetic ingredient. The Panel decided to reopen this report in November 2003 to consider the sensitization potential of propyl gallate as seen in patch testing result at lower concentrations than originally thought. Based on the data evaluated during the rereview, the Panel concluded that propyl gallate is safe in the practices of use described in the amended safety report at a concentration of less than or equal to 0.1 percent.

So, it came down by an order of magnitude. Newly found studies included updated regulatory limits for human and animal consumption, in vitro genotox, in vitro developmental and reproductive tox. Studies on estrogenic and in vitro effects on tumor cells, ocular irritation, numerous clinical patch test reports. Of note, there's in vitro developmental and reprotox as well as developmental tox in zebrafish not present in the amended report.

Ocular irritation reports that were positive were found. In 2023 the VCRP had 86 reported uses down from 164 uses 20 years earlier. Maximum reported concentration was 0.012 percent in eyeliners compared to 0.1 percent in other personal cleaning products as reported in 2003. So, the question is do we open or not reopen this? I waivered on this.

DR. BERGFELD: (Inaudible).

DR. COHEN: I was ambivalent about it. I needed more advice from the Panel.

DR. BERGFELD: So, in '85 we said 0.1 and earlier -- later we said in the second review, we said 0.1. So, what would change your mind?

DR. COHEN: You mean, why reopen it?

DR. BERGFELD: Yeah.

DR. COHEN: Yeah.

DR. TILTON: Yeah. I guess I didn't see a reason to reopen. There is new data but in going through it, it did not present a toxicity concern, or it already confirmed data that was in the report. I didn't feel like there was anything additional that couldn't just be summarized in my case.

DR. ROSS: I was sort of in agreement with that. I went through it. There was new ocular studies showing some irritation. There was a new in vitro and superficial DART data. There was new ADI value. But if you look at it, I mean the uses are way down and we're still at the same concentrations and it's in line with the 2007 conclusion, so I came down as a do not reopen.

DR. COHEN: I'm okay with that. It was the ocular, and I didn't know impactful the zebrafish was going to be so we'll do do not reopen.

DR. TILTON: A lot of them are just concentration data and ocular irritation was (inaudible) and the in vitro/in vivo studies were at higher concentrations.

DR. ROSS: Yeah.

DR. COHEN: So, tomorrow, I report on paraphenylenediamine, yeast, fatty amphocarboxylates, 4-chloro-2-aminophenol, cholesterol, boric acid, and hydrolyzed collagen. Any further comments on any of those?

DR. BERGFELD: Well, I think we have hot items that -- we have the prostaglandins, you have that one, yeast, and the phenylenediamine. The rest of it should fall in line.

DR. COHEN: The yeast could go pretty quickly tomorrow.

DR. BERGFELD: Could go if they agree with all the movements the ingredients up to safe.

DR. ROSS: It's going to be the amphocarboxylates and the prostaglandins.

DR. COHEN: Even the amphocarboxylates, we have an IDA for that.

DR. ROSS: Yeah.

DR. COHEN: And I thought that was --

DR. ROSS: Is that Don? Are you presenting that one or is --

DR. COHEN: Yes.

DR. ROSS: Yeah.

DR. COHEN: And I have some comments in here about concerns about read across for mixtures and concerns about read across for certain endpoints like DART and the read across was not supported for betaines. Okay. And then we get into the IDA.

MS. FIUME: It may not.

DR. COHEN: I think your advice to IDA that was right on as opposed to tabling it which was my initial gut when I was reading it.

DR. ROSS: That's what I thought.

MS. FIUME: It's difficult to follow the process because we rarely have a revised draft report, but that table from last time put everything on hold and we couldn't go forward with any action items that last time. So, it gets confusing.

DR. COHEN: Okay. Good. Are we calling it? Are we calling it before 3:00 p.m.?

DR. ROSS: Are we good?

DR. COHEN: We can go off the record now, right?

Full Panel – June 4, 2024

DR. BELSITO: So the Expert Panel first published a review of Propyl Gallate in 1985. We concluded on the basis of the available information present in a report that Propyl Gallate was safe as a cosmetic ingredient at concentrations not exceeding one percent. We decided to reopen the report in 2003 to consider a sensitization potential of Propyl Gallate based upon patch testing results at lower concentrations than originally thought. And based on the data that we saw then in the rereview we changed our conclusion to Propyl Gallate is safe in the present practices of use as described in the amended safety report at concentrations of less than 0.1 percent. And that was published in 2007. Because it's been 15 years since that time, we're looking at this again to determine whether to reopen or not.

A number of new studies have been found on human and animal consumption, in vitro genotox studies, in vitro developmental and repro studies, studies on estrogenic and in vitro effects on tumor cells, in vitro dermal irritation, ocular irritation, numerous clinical patch test studies, in vitro developmental and repro as well as some developmental studies on zebrafish that weren't in the original report.

And we looked at all of this, and we also wondered why other alco-gallates that are out there were not included in any other rereviews. And based upon that we thought we should reopen to add additional alco-gallates that were no-brainers, and to evaluate the new DART and genotox data and discuss that.

DR. COHEN: So, we went back and forth whether the final conclusion would change. We didn't think it would change, but based on your discussion and your suggestion was to bring on other alkyl gallates. I think doing that would simplify things, so I'll second that motion so we can organize the gallates together.

DR. BELSITO: Yeah, I thought also the prior discussions in the two preceding reports were grossly insufficient.

DR. BERGFELD: Okay, we can call the question if there is no further discussion, all in favor of reopening the Propyl Gallate?

DR. SNYDER: I concur.

DR. BERGFELD: Thank you, unanimous. Moving on to Boric Acid.

DR. COHEN: Can I just one off a question?

DR. BERGFELD: Go on.

DR. COHEN: Bart, are we obliged to publish every report in the National Journal? Is there a contractual obligation?

DR. HELDRETH: No, it doesn't have to be that journal (inaudible).

DR. COHEN: Because, you know, getting the gallates all together, the gallates are a difficult group of allergens to cope with in the contact dermatitis world. This might be a very nice report to go in dermatitis as opposed to the IJD.

DR. BERGFELD: Or somewhere in the portal.

DR. COHEN: You know, we struggles with these reactions on patch testing.

DR. BELSITO: Yeah, I mean, it's just that I think some substance of the article might not be appropriate for dermatitis. It may be better for the Panel or a subset of the Panel to write a shorter article dealing specifically with the sensitization irritation issue in a different discussion.

DR. COHEN: They might be interested. We could do a test run on it.

DR. BELSITO: We could send it, yeah.

DR. COHEN: Okay.

DR. BELSITO: I have no objection to it. I agree that I think a lot of that patch test that are called positive the gallates are irritants.

DR. COHEN: Yeah. Okay.

DR. BERGFELD: All right, moving on to the next ingredient, Boric Acid, Dr. Cohen.

MARCH 2026 MEETING – DRAFT REPORT STAGE

Belsito Team – March 12, 2026

DR. BELSITO: Okay, Alkyl Gallates. There was a Wave 2 to this, so let me look.

DR. EISENMANN: Maximum use concentration got decreased from 0.2 to 0.1 in face and neck products. That's what Wave 2 was.

DR. BELSITO: Okay. Yeah, nothing. Okay. So, we first published a report on Propyl Gallate in '85. The Panel concluded that it was safe as a cosmetic ingredient in concentrations not exceeding 1 percent. At that point, I think we weren't getting concentrations of use, so we're setting concentration limits if we were concerned about sensitization or irritation or another endpoint.

In 2007, we published a report with the conclusion that Propyl Gallate was safe in the present practices of use as described in the safety assessment, at concentrations less than or equal to 0.1 percent. We reconsidered the safety of Propyl Gallate in 2025, determined to reopen the assessment because of new tox data and to include other Alkyl Gallates that hadn't been reviewed, Caprylyl, Dodecyl and Ethylhexyl.

So, that's where we are. We have a RLD submitted by the FDA in 2025. Propyl Gallate is in 1,127 total formulations, and the other ingredients are used in 21 formulations or less, and no concentrations of use were reported for the other Alkyl Gallates that had 21 formulations or less.

As Carol pointed out, the report that it's used up to 0.2 percent in face and neck products throughout this report has been corrected, in Wave 2, to 0.1 percent. And then just a few questions in the document.

On PDF Page 22, Priya, it says in a porcine skin with approximately 14 percent percutaneous. Were these miniature swine, because that's the best skin model for absorption in humans; do you know? Or it just said pig skin?

MS. FERGUSON: I think it said pig skin.

DR. BELSITO: Okay.

MS. FERGUSON: But I can go back and double check.

DR. BELSITO: Yeah, just check; because if it says miniature I think that that is good to have in there.

MS. FERGUSON: Gotcha.

DR. BELSITO: So we have a good multi-generational oral exposure in rats with no reproductive effects, so I think we have the DART effects covered. Then the intraperitoneal DART, I think, is not relevant. The zebrafish, dose-dependent statistical significant malformations, altered hatching, but they were injected with 1 to 50 parts per million of Propyl Gallate. Did you make much of that, Paul, the zebrafish? This is PDF Page 24.

DR. SNYDER: No, I didn't make much of that.

DR. BELSITO: Yeah, I thought the multi-generational studies sort of covered that.

DR. SNYDER: Yeah, especially in lieu of having that data, yeah.

DR. BELSITO: Yeah, okay. And then, I guess, we'll have the discussion about discontinued studies and the genotoxs. There were statistically significant increases in sister chromatid exchange observed in CHO cells. And we're told by Sam that that's not a good study, right? So, I guess we're going to try and come up with a boilerplate for these studies that have been discontinued.

Estrogenic effects. I don't even think we need to deal with it in the Discussion, given the negative one-generation repro study.

DR. SNYDER: I agree with that, too.

DR. BELSITO: Okay. In terms of the clinical studies, these Alkyl Gallates are notorious irritants, and I just can't put much belief in a lot of the positives that were reported. I think a lot of the positive reactions, I need to see the strength of them that were irritants. I rarely see true positive reactions to Gallates.

The depigmentation, that case report, again, I don't know if we bring into the Discussion. But this woman clearly had a very, very strong reaction to the Gallate, and I think it's what's called post-inflammatory hypopigmentation, and it's not truly an effect on melanogenesis; it's killing off of the melanocytes due to the severity of the toxic reaction. So, I mean, it's depigmentation, we probably should mention it in the Discussion, I don't know.

But point out that, given the severity of the allergic reaction noted, it's more than likely in this individual that the hypo/depigmentation was a post-inflammatory effect and not a direct effect on melanogenesis. I don't know, Paul, Curt, Allan, would you even mention it in the discussion? We always do mention effects on pigment.

DR. SNYDER: Yeah, I think we have to address it. But I think you've addressed it well, just saying that the Panel's interpretation of the single case report was not likely a direct effect; it was a post-inflammatory because of other -- you know, as you stated.

DR. BELSITO: Yeah, I mean, she developed vesicles and ulcerations. She lost her epidermis, which is where the melanocytes are, right? So, it's an effect of the response.

So, Discussion, heavy metals, impurities, the estrogenic effects we're not even going to mention, right? So let me get rid of that. We have a negative two-gen reproductive study. We have plus-or-minus genotoxicity, but a two-year carcinogenicity study, which is negative. Lots of patch test reactions, but the -- I don't know how you want to say this. The experience of expert opinion is that many of these may have been irritant? I don't know exactly how you want to say it. The depigmentation was likely post-inflammatory and not a direct effect on melanogenesis.

DR. SNYDER: That sounds perfect, yeah.

DR. BELSITO: And, conclusion, safe when formulated to be non-irritant. That's what I have. Paul, Curt, Allan?

DR. KLAASSEN: Yeah, on the positive side, this is a GRAS ingredient as a food additive. So, that gives some --

DR. BELSITO: It is not.

DR. KLAASSEN: Huh?

DR. BELSITO: It is not.

DR. KLAASSEN: Oh, I thought I read that it was.

DR. BELSITO: It's used in homeopathic medicine, but it's not a food, right, Priya?

DR. KLAASSEN: I don't know, in my notes here I put that it was, but maybe I screwed it up.

MS. FERGUSON: It's used as an antioxidant in food and food contact applications.

DR. KLAASSEN: Right.

DR. BELSITO: But the plant itself is not considered GRAS or a food, right? It has medicinal uses, and it has regulations in the EU for the composition as a medicinal use, was my understanding.

DR. EISENMANN: Propyl Gallate?

DR. KLAASSEN: Yeah, I think one of the gallates; I thought it was Propyl Gallate, not all of them.

DR. BELSITO: I'm sorry.

DR. KLAASSEN: Yeah, I got all three are allowed.

DR. BELSITO: I had, like, a brain or whatever. I was back to thinking about Willow. Yeah, the gallates are used as antioxidants in foods, particularly, like margarine, it's used in. So, the FDA does allow it to be used in food substances. Did we capture that in non-cosmetic uses? I don't remember.

MS. FERGUSON: It's in the non-cosmetic use section.

DR. KLAASSEN: I think it's an important thing to add.

DR. BELSITO: To the Discussion?

DR. KLAASSEN: You know, to the summary.

DR. BELSITO: Yeah.

DR. KLAASSEN: It always gives me a fair amount of confidence when I know that one of these compounds is also a GRAS ingredient that the FDA, in essence, can say we can have it in food, as a confidence builder.

DR. BELSITO: Yeah. Okay. So, add that Propyl Gallate can be used as an antioxidant in foods and as an essential oil in various food products. Okay, that goes into the Discussion. Anything else on this before we move on?

DR. SNYDER: Nothing for me.

DR. BELSITO: Allan? Curt?

DR. RETTIE: I had a logP discussion with people, but I'll just send that to Priya in my notes.

DR. BELSITO: Okay. What about the logP?

DR. RETTIE: It's got to be the wrong numbers in Table 2 for Dodecyl. I sent an email around to the Panel and didn't get anything back. It's a minor issue.

DR. BELSITO: Okay.

Cohen Team – March 12, 2026

DR. DAVID COHEN: And now to our last one, Gallates. This is a Draft Amended Report on Alkyl Gallates, which includes Propyl Gallate and the additional ingredients, Caprylyl, Dodecyl, and Ethylhexyl Gallate. These ingredients are gallic acid esters that function primarily as antioxidants in cosmetic formulations. Propyl Gallate was originally reviewed by the Panel in 1985, with the conclusion that it was safe as used in cosmetics at concentrations up to 1 percent. In 2007, the Panel amended that conclusion to state that Propyl Gallate is safe in the present practices of use at concentrations less than or equal to 0.1 percent, primarily based on concerns regarding sensitization potential.

This report reopens the assessment to evaluate new toxicologic information and to include additional Alkyl Gallate currently reported in use. With respect to current exposure, Propyl Gallate is used in over 1,000 cosmetic formulations while the other Alkyl Gallates have substantially fewer uses. Concentrations have been reported for Propyl Gallate. Updated Wave 2 concentration of use data indicate maximum recorded concentration of Propyl Gallate in leave-on face and neck products is 0.1 percent, as opposed to, I guess, previous 0.2 percent. This updated value aligns with the concentration limits of the 2007 amended report.

Propyl Gallate is also reported at lower concentrations in eye products, lip products, and baby products. We have sensitization data. We have HRIPTs. Propyl Gallate, we have animal sensitization studies demonstrating sensitization potential across the Alkyl Gallate class, with Dodecyl Gallate appearing to be the most potent sensitizer.

So, we have this historic limitation of less than 0.1 percent, and do you think we could read across amongst the other alkyl gallates appropriate for sensitization endpoints? I'm not sure.

DR. ROSS: Well, the read-across group didn't meet for this meeting, but my read of this, when I list out the logPs and the solubility, going from Propyl -- Propyl has a logP of 1.5 or 1.8, okay? The solubility's at 3.5. Caprylyl, which is basically Octyl, had a logP of 3.6. The solubility's 0.036.

So, it's possible you might be able to read across to Caprylyl based on that pharmacokinetic -- I should say the physical/chemical data. But Dodecyl is a real outlier. The logP is 5.3. It's insoluble, so I would say you shouldn't -- it would be very difficult to read across from Propyl to Dodecyl. We don't have any data on Ethylhexyl, so that's out as well at this point, but Caprylyl is a possibility of reading across, so I think that's still in play.

That's my call. EFSA, European Food Safety Agency, they used to group these together and more recently they've taken them apart, mainly because they didn't have toxicokinetic and metabolic data on some of them. But just looking at the logPs and solubility, I would say no to Dodecyl, Caprylyl is a possibility. And Propyl looks okay to me at low concentrations of 0.1 percent. I don't know about anybody else's opinion.

DR. DAVID COHEN: You're talking about Propyl Gallate?

DR. ROSS: Yeah. Across the board it looks okay. We have a lot of data. I didn't see any issues at 0.1 percent, and other people can comment.

DR. TILTON: I guess, Dave, similar to the discussion we just had about ocular, I did make a note here, too, that -- I mean, it's difficult when it's only tested when applied neat and you have severe ocular irritation.

DR. ROSS: I thought we had some lipstick formulation concentrations less than 1 percent that were not irritant in rabbit eyes. Did I conjure that up, or is it real? Let's have a look.

DR. TILTON: I thought I had understood that that study was inconclusive, which is why they --

DR. ROSS: Maybe, let me have a look.

DR. TILTON: -- moved in vitro.

DR. ROSS: Yeah, that's the case. Your comment is well taken, because, yeah, these neat studies --

DR. TILTON: Or the in vitro was inclusive.

DR. ROSS: Okay, I'm getting there. Ocular, okay. A lipstick formulation containing less than 1 percent Propyl Gallate was also considered to be non-irritating in rabbit eyes.

DR. TILTON: And that was at 1 percent?

DR. ROSS: Yeah. It said less than 1.

DR. DAVID COHEN: Are you on 29?

DR. ROSS: That's PDF -- what is that?

DR. TILTON: Is it 37 in the table?

MS. FERGUSON: No, it's Page 29. It's an italicized text so it wouldn't be in the table.

DR. TILTON: Oh, okay.

DR. ROSS: Page 29. I'm so much slower than Priya at getting to the right answer, you know, and this is typical. Thanks, Priya.

DR. DAVID COHEN: Really a problem with that statement, is a lipstick formulation containing less than 1 percent. Is that 1,000th of a percent, or is that 0.09 percent? What does that mean?

DR. SAM COHEN: The first paragraph there in italics says there's six cosmetic formulations, each containing 0.003 percent, were evaluated.

DR. DAVID COHEN: That is way off from the max use.

DR. SAM COHEN: Exactly. And then the lipstick formulation was less than 1 percent.

DR. ROSS: So it's not specific, yeah.

DR. DAVID COHEN: I don't know, I almost don't even know what value that sentence has.

DR. ROSS: I went down that road at the last meeting, yeah. I tried to get things that didn't have specific concentrations out of here, but it was felt they still had value.

DR. DAVID COHEN: It's a little (inaudible) to the package, but.

DR. ROSS: So, Susan, your point was in the epi-ocular, which is the bovine corneal opacity? Yeah, okay.

DR. TILTON: Sorry, I'm in the wrong report; I'm trying to catch up.

DR. ROSS: Is that stuff in the table as well, or not? Look at my notes, I guess.

DR. BERGFELD: I thought that the Wave 2 gave us new concentrations that were very, very low.

DR. ROSS: Wilma is usually right. Let's have a look.

DR. DAVID COHEN: Except --

DR. SAM COHEN: In Table 3, they're listing as 0.03.

DR. DAVID COHEN: For which one?

DR. SAM COHEN: For Propyl Gallate for eye area exposure type, it's listed as .02 percent.

DR. BERGFELD: 0.2, yeah.

DR. DAVID COHEN: But did I make a mistake in my opening recitation, indicating that the max use was .1?

DR. EISENMANN: That is the correct max use. That's the only thing that changed in Wave 2. It went from 0.2 -- that is correct, it's 0.1.

DR. DAVID COHEN: It's 0.1 even though Table 3 has it as 0.2?

DR. EISENMANN: Correct.

DR. DAVID COHEN: That's the Wave's correction. Yeah, because I'm looking at the table and I'm like did I make a mistake on this?

DR. EISENMANN: No.

DR. DAVID COHEN: Okay.

DR. ROSS: No, that was in Wave 2, as Carol says. Yeah.

DR. EISENMANN: Correct. And that was the only change in the concentrations of use in Wave 2, that one change.

DR. DAVID COHEN: Which is helpful because it harmonizes with the prior conclusion.

DR. EISENMANN: Correct.

DR. DAVID COHEN: It makes it easy to clear Propyl Gallate, right? And so, the question is what can we drag along, or perhaps read across is another term?

DR. ROSS: Possibly Caprylyl, not Dodecyl, in my opinion.

DR. BERGFELD: David, you said it was a solid?

DR. ROSS: Insoluble, water insoluble.

DR. BERGFELD: Oh, water insoluble, that's what you said.

DR. ROSS: It was just comparing water solubility. Yeah. So, I think the values, Wilma, were -- solubility gram per liter was 3.5 for Propyl, 0.036 for Caprylyl and Dodecyl, forget about it, it was insoluble, so.

DR. BERGFELD: Okay. I wonder about insoluble materials, how they go through the skin? Not well, I would think.

DR. ROSS: So, I could be persuaded on Caprylyl, I guess, but not Dodecyl. And Ethylhexyl, I have no data, so.

DR. SAM COHEN: Don't we need ocular irritant information on levels that are more comparable to the use for eye irritation?

DR. ROSS: I think Susan raises an excellent point. Yeah, if we have no specific concentrations in that earlier study, then I think we do.

DR. SAM COHEN: But that's much lower than the use level.

DR. ROSS: Much lower, yeah.

DR. DAVID COHEN: So, we need? So, we're going out with -- let me just make sure this is where we are in the -- so, this is an Insufficient Data Announcement, no? Insufficient Data Announcement requesting ocular irritation at max use around the eye.

DR. SAM COHEN: Right.

DR. ROSS: For Propyl Gallate, yeah.

DR. DAVID COHEN: For Propyl? And we're asking for all of the, right?

DR. ROSS: Yeah, we could ask for all of them because there's nothing there.

DR. SAM COHEN: And for Dodecyl we basically need everything.

DR. DAVID COHEN: Could you play it out for me? Dodecyl we want irritation and sensitization.

DR. SAM COHEN: Yeah. Tox data, genotox, repeat tox.

DR. ROSS: DARTs.

MS. FIUME: Can I clarify for the ocular? So, there's only two that have use in eye-area products. You have concentration of use for Propyl, and you don't have concentration of use for Ethylhexyl.

DR. DAVID COHEN: That's a good point.

MS. FIUME: Not that you can't ask for it, but I don't know what you would get for it.

DR. DAVID COHEN: Propyl and what?

MS. FIUME: Propyl and Ethylhexyl. And Ethylhexyl doesn't have a concentration of use in the table at all. There's no concentration of use for Ethylhexyl.

DR. ROSS: So, the only two with ocular uses, Monice, are Propyl and Ethylhexyl?

MS. FIUME: Correct.

DR. DAVID COHEN: Now, I'm sure when I make that statement we're going to go back to the report. so I just want to make sure. So, our ocular tox is at?

DR. SAM COHEN: 0.003.

DR. ROSS: 0.003 percent, not irritant.

DR. SAM COHEN: And neat is 0.02.

DR. DAVID COHEN: So it's 0.003 percent, and max use is 0.2 percent?

DR. SAM COHEN: 0.02.

DR. DAVID COHEN: Okay. So, it's an order of magnitude off.

DR. ROSS: Is that right, 0.02, Sam, is that?

DR. TILTON: I mean, that is listed for eye area. You know, eyeliners.

DR. BERGFELD: That's in Wave 2.

DR. ROSS: Yeah, I got it.

DR. DAVID COHEN: So, am I right, it's an order of magnitude off? And the data that we have in the report of being less than 1 percent has no tangible value to us right now?

DR. ROSS: Unless you knew it was 0.9, or 0.8, or 0.7; unless you knew a specific concentration.

DR. DAVID COHEN: But that would clarify an IDA, right?

DR. ROSS: Yeah. Yeah, that would work.

DR. DAVID COHEN: That would clarify an IDA. So, I have ocular irritation at max use around the eyes for Propyl and Ethylhexyl. For Dodecyl we need basically everything, irritation, sensitization, acute tox, genotox, DART, right? What else am I missing?

DR. ROSS: Yeah. Dodecyl you would need acute tox, dermal irritation, ocular irritation, DART, and genotox. So, I think that covers it, right?

DR. DAVID COHEN: Do we have dermal tox or no?

DR. ROSS: On Dodecyl you have no dermal tox or acute toxicity at all; although, you've got some repeat dose, but you've got no dermal or oral acute. I mean, you know, you just need a lot of things for Dodecyl.

DR. DAVID COHEN: That's interesting, I wouldn't have expected this at first glance to come to an IDA, but I see why. These things have been around a long time.

DR. ROSS: I think on Propyl you're very, very close here.

DR. DAVID COHEN: I do, too.

DR. ROSS: And who knows, tomorrow, there may be an argument for reading across the whole group. We'll just have to see how that plays out.

DR. DAVID COHEN: Yeah. I'll tell you from a purely clinical perspective, the Gallates come up a lot in patch testing. They come up positive a lot. And the question is, it is really hard to apply clinical relevance to them. You know the argument that Don made today when I was talking about the linalool positive reactions, was what's the relevance? This is the caricature of patch test relevance when you see positive reactions, because they come up all the time.

DR. SAM COHEN: Are they ever for real?

DR. DAVID COHEN: Huh?

DR. SAM COHEN: Are they ever for real, clinically?

DR. DAVID COHEN: I think rarely, sometimes. You don't know that, Sam, for months, right? Because you read the patch test, you give them the advice, and some people come back and tell you that they found it in products, they felt elimination of the products was helpful; but I find a lot of the times, or maybe even most of the time, I can't assign good clinical relevance, despite the fact that we get a positive patch test reaction to it. I'll be curious to hear what Don thinks about it, too.

MS. FIUME: David, can I ask, did you ask for repeated dose for Dodecyl, repeated dose toxs? I lost the list.

DR. SAM COHEN: DART would cover that adequately, I think.

DR. ROSS: Well, we don't have any -- Dodecyl, you've actually got some repeat dose oral in here.

MS. FIUME: You have a 14-day study.

DR. ROSS: Yeah, I think you're fine there.

MS. FIUME: Okay. I thought you had said it, and I just wanted to point out there was a 14-day study. Okay, sorry about that.

DR. DAVID COHEN: I don't know if I really covered everything here.

DR. TILTON: We don't have method of manufacturing for everything but Propyl.

DR. ROSS: Propyl we have, right?

DR. TILTON: Yes.

DR. DAVID COHEN: So, you want a method of manufacturing for everything but Propyl?

DR. ROSS: Yeah.

DR. TILTON: Yeah.

DR. DAVID COHEN: You have impurities on them. I'm just pushing back, is it going to change anything here? But, I mean, we're in an IDA, we can ask to make the report complete.

DR. SAM COHEN: Yeah.

DR. TILTON: I mean, the chemistry, as Dave said, is so -- there's a range.

DR. DAVID COHEN: Okay.

DR. TILTON: And we're potentially considering read-across. I'm not sure if that will work, but --

DR. SAM COHEN: Especially soluble versus insoluble, that pretty hard to read-across.

DR. TILTON: Yeah.

DR. DAVID COHEN: Wait a minute, we have Caprylyl, Dodecyl, Ethylhexyl. The chart has three, not four, right? The initial data profile -- oh, it has all of them. And you think an argument about read-across could be mounted?

DR. ROSS: I don't know, I doubt it. You might have them go for Caprylyl. I wouldn't have thought they would go for Dodecyl, and you just have no data on the Ethylhexyl. I think that's where it'll end but, hey, I've been wrong many times before.

DR. DAVID COHEN: I think rarely here. Okay. Any other needs?

DR. TILTON: We currently have no concentration of use either, right, for everything but Propyl?

MS. FIUME: That's correct.

DR. ROSS: Yeah.

DR. DAVID COHEN: Okay, yeah, no, I added it on. Any other needs? So, I have ocular irritation at max use around the eyes for Propyl and Ethylhexyl. For Dodecyl, irritation and sensitization, acute oral and dermal tox, genotox and DART, method of manufacturing for all but Propyl, concentration of use for everything but Propyl.

DR. TILTON: And outside of the question about ocular irritation at max use, it really only -- because it was such a severe ocular irritant when neat, it's hard to scale from that.

DR. DAVID COHEN: (Audio skip).

DR. TILTON: Otherwise, I felt Propyl, as we've discussed, is pretty close to safe as used.

DR. ROSS: But it's the first time through, we should ask for it. And I think you need something to clear it, so let's hope we get it.

DR. DAVID COHEN: Once we've articulated this issue about the ocular tox, not getting it is going to be an issue.

DR. SAM COHEN: Well, then we just say it's safe for use for all these other categories, but not for around the eyes.

DR. DAVID COHEN: Gosh, that's not a very common conclusion we make.

MS. FIUME: Actually, a lot of times you'll say safe when formulated to be non-irritating.

DR. ROSS: Yeah.

DR. DAVID COHEN: Yeah, but it -- I guess I recall using -- we certainly use that plenty, but do we use that just to cover eyes?

MS. FIUME: Dermal and eye; it could be either irritation.

DR. DAVID COHEN: Well, that may be a reasonable solution tomorrow, right?

DR. ROSS: Mm-hmm.

DR. DAVID COHEN: Okay. Do we want to go with that for Propyl?

DR. ROSS: Safe as used when formulated to be non-sensitizing.

DR. DAVID COHEN: No, no, no, no, non-irritating.

DR. SAM COHEN: Non-irritating.

DR. ROSS: Non-irritating.

DR. DAVID COHEN: Because, also, by the way, I don't think we need to, do we put a concentration in the Conclusion?

DR. BERGFELD: No.

DR. DAVID COHEN: We don't need to because we already have it at 0.1 and we just mentioned it in the Discussion that it's 0.1, right? The second wave created a 0.1 ceiling.

DR. ROSS: Just playing devil's advocate to that argument for a second; if this is first time through, maybe you ask for the ocular data and if you don't get it, Plan B, next time through is just exactly what you said, safe when formulated to be non-irritant.

DR. DAVID COHEN: I'm playing counter devil's advocate. This is now in the minutes, and the companies say, well, if we don't give them anything we'll just get a safe as used when formulated to be non-irritating.

DR. ROSS: Oh, okay. Well, we can go that way. I'm just trying to think the length of time it would take to get to that point either way, and I think it's going to be the same.

DR. BERGFELD: Six months.

DR. ROSS: Yeah. It seems like a long time for a --

DR. DAVID COHEN: I guess, Dave, legitimately, maybe someone pulls that report out at the less than 1 percent on the eye, and we actually get the concentration.

DR. ROSS: It can go either way, I think.

DR. SAM COHEN: Well, because of all the data requests we're asking for everything else, this is going to be an Insufficient Data Announcement anyway, so might as well ask for the ocular.

DR. DAVID COHEN: Yes.

DR. ROSS: I agree with Sam, yeah.

DR. DAVID COHEN: Since they’re all put into the same Alkyl Gallate, and it's not just a Propyl Gallate report anymore.

DR. SAM COHEN: Right.

DR. DAVID COHEN: Okay. We can have a lively interaction with that tomorrow.

DR. BERGFELD: Be ready to compromise.

DR. DAVID COHEN: Aren't I a compromiser when it's appropriate? Now, I have one request, which is, I was not here for the totality of the Use Tables, Airbrush, Genotox and the Phthalates.

Full Panel – March 13, 2026

DR. DAVID COHEN: Okay. This is a Draft Tentative Amended Report for Caprylyl Gallate, Dodecyl Gallate, Ethylhexyl Gallate and Propyl Gallate. As a reminder, Propyl Gallate was previously reviewed by the Panel and the existing conclusion is that Propyl Gallate is safe in cosmetic concentrations up to 0.1 percent. Based on the updated use information, the current maximum concentration of use for Propyl Gallate is, again, 0.1 percent. So, in that respect it currently aligns with the prior conclusion.

However, my motion is for an Insufficient Data Announcement for Caprylyl, Dodecyl, Ethylhexyl and Propyl, with the following data needs: ocular irritation data for Propyl Gallate that is relevant maximum use concentration, particularly for reported eye-area uses, maximum concentration of use for Caprylyl, Dodecyl, and Ethylhexyl. If eye-area uses are confirmed for any of the newly added gallates, ocular irritation at relevant maximum concentration, (inaudible) concentration of use.

And we just want to recognize that Propyl Gallate is the best supported ingredient here, but the eye-area concentration of use and the eye data we have are not aligned. That's my motion.

DR. BERGFELD: Don, any second or comment?

DR. BELSITO: No, we had a different conclusion.

DR. DAVID COHEN: What was it?

DR. BELSITO: We concluded that it was safe when formulated to be non-irritating. And in terms of your request for concentrations, again, we fall back to the idea that the concentrations are the same as for other ingredients in the report.

DR. DAVID COHEN: Yeah, Don, that's -- look, it's not far from where we landed. But in the report I think the eye irritation data was almost an order of magnitude off. There was one comment -- and I'm doing this from memory -- that less than 1 percent was non-irritating. We don't know whether that's .09 or .0009, and the data that we did have was much, much lower than the max use concentration around the eye.

I suppose if you're acknowledging that data gap, you're getting around it by the provision of non-irritating.

DR. BELSITO: Yeah.

DR. ROSS: And so, could I ask -- yeah. No, I mean, actually, we discussed that, David, prior to getting to this conclusion. So, I think it's certainly a possibility. You put all of them in the same boat, Don? You were Caprylyl, Dodecyl, and Ethylhexyl as well?

DR. BELSITO: Yes.

DR. ROSS: So, I'll ask your read-across. We didn't have a read-across meeting before this CIR meeting, but you thought you could read-across to those, doctors Rettie and Klaassen, I'll ask?

DR. BELSITO: For irritation, I mean, yeah.

DR. SNYDER: Don, ours was safe as used when formulated to be non-irritating.

DR. BELSITO: That's correct. That's what I said.

DR. SNYDER: Oh, I'm sorry.

DR. ROSS: I mean, we looked at the possibilities of read-across. We thought we could maybe drag Caprylyl in. But we thought there was a big jump to Dodecyl, and we didn't have any data on Ethylhexyl. So, we hung up on those two.

DR. DAVID COHEN: Yeah, I don't think we have sensitization on Ethylhexyl, right?

DR. ROSS: No, you haven't got much on Ethylhexyl. And actually, when you look at difference in endpoints, dermal sensitization was more pronounced with Dodecyl.

DR. BELSITO: You know, I have to say that that sensitization data -- hold off on saying sensitization. Positive patch test. And my expert opinion is that most of the positive patch tests are irritant with these Gallates.

DR. ROSS: Yeah.

DR. DAVID COHEN: We spoke about it yesterday. It is a group of chemicals that we can always count on being positive on patch tests when they're tested, and the relevance of that reactivity is still in question. The problem is that -- I don't disagree with you, Don, it's just I don't know the relevance of those things very well. But we do see the positive patch tests on those. That's why, for a number of reasons, we didn't read across on that.

DR. ROSS: And just one quick comment on the physicochemical data -- and Allan and Curt can comment -- but the logPs, for example, for Propyl partition coefficients, were in the area of 1.5, and for Dodecyl, 5.3. It's a huge difference. And the solubility, 3.5 grams per liter for Propyl and insoluble for Dodecyl. So, I couldn't quite get there for those two.

DR. RETTIE: I agree with you there, Dave. There's an error in Table 2, almost certainly, under Dodecyl. The logPs, the 3.2 there is not a good number. It's lower than one of the others, the Caprylyl, and that just can't be so. It's a thousand-fold difference in terms of lipid-water solubilities, and so I take your point there, Dave.

DR. ROSS: Yeah. So, we were bringing in Caprylyl, but we --

DR. BELSITO: So then, I guess my question is, if you don't feel we can read across, why in June 2024, did we bring all these other ingredients into the report?

DR. ROSS: That's a good question, yeah.

DR. BELSITO: Because that seems to me that we had agreed that they could be read across, right? Because adding ingredients was supposed to be a no-brainer.

DR. RETTIE: We weren't looking at these differences, and I was a bit surprised that they were as big as this. I only got my attention drawn to it when I saw the error in Table 2. Perhaps we should not have brought in certainly the Dodecyl, but as a grouping when you look at it, just on the face of it, it looks like it could be okay. But I'm not comfortable with the Dodecyl being grouped in with the others.

DR. ROSS: And it could be we run into similar problems with the Ethylhexyl. I mean, basically, that's an Octyl, right, I mean, when you look at that.

DR. RETTIE: Well, that's Caprylyl, right? That's C8, so.

DR. BELSITO: What endpoints would you be concerned about not reading across to with these structures?

DR. ROSS: Well, quite a few of the endpoints. If you're doing toxicity, if you're doing -- it looks like there's some different data, whether it's sensitization, Don, or whether it's irritation.

DR. RETTIE: Due to differences in distribution, I guess, would be what we said before.

DR. ROSS: And I think differences in distribution could affect quite a few of the endpoints. Anyway, that was just my call when I looked at it.

DR. DAVID COHEN: Yeah, we spent a lot of time talking about it.

DR. BELSITO: I mean, in terms of sensitization, if you look at the molecule, do you think the R group is the important part of a sensitizer? Or do you think that it's the Gallate Acid?

DR. ROSS: That's a good question, and it's probably the Gallate Acid, but I don't know for sure.

DR. BELSITO: I don't think the R group is going to affect sensitization.

DR. ROSS: Yeah, I think you're probably right.

DR. RETTIE: I tend to agree.

DR. ROSS: Getting back to Allan's point, if you're getting such huge distribution differences on solubility and partition coefficient, it's going to affect a lot of endpoints, almost every endpoint we have in this list.

DR. BELSITO: But the distribution becomes less absorbed, right, with a higher R group?

DR. RETTIE: Yes.

DR. ROSS: Yes.

DR. BELSITO: So, then can't you use Propyl, which would be more absorbed, to clear the higher molecular weights?

DR. RETTIE: That would be something to consider; I'm not absolutely certain what I think of that.

DR. ROSS: Just walking through it myself.

DR. DAVID COHEN: Isn't the sensitization rate, though, different between these things, with Dodecyl being the highest? I mean, I don't think they're all uniform. They're not, as a matter of fact.

DR. BELSITO: David, let's get rid of the word sensitization, okay? Because, in my opinion, you might say that relevance you don't know; to me they're irrelevant, and often they're macular erythema, and to me they're an irritant.

DR. DAVID COHEN: I don't necessarily agree with that most of them are macular erythema. I do see plenty of what I would consider positives, but I really don't know the relevance. And so, I just don't feel that comfortable. Just because I don't know what the relevance are of those things doesn't mean I could just clear it based on that.

And, you know, it's an issue all around. Everyone's head spins from patch testing to the Gallates, right, that there's no uniform agreement on this.

DR. BELSITO: But you have the patient bringing in all of their products, and it's not on the list at all.

DR. DAVID COHEN: It's usually not on the list.

DR. BELSITO: They have no evidence of using it. And if you do a ROAT, as I've done, with the patch-test concentrations, they're negative. So I have to conclude that most of the reactions I see are irritant.

DR. DAVID COHEN: Or with products that (inaudible). Yeah, I just -- this is -- that's sort of a different conversation than this. I don't disagree with you, but I don't know if I could take just that personal experience and take it all the way through here.

DR. BELSITO: Well, I mean, a lot of times when you're looking at determining safety and risk, you have to use expert opinion, right?

DR. DAVID COHEN: I agree. And I think if we just had Propyl Gallate I could buy the safe as used when formulated to be non-irritating. I just don't know how to drag the rest across.

DR. BELSITO: Well, you look at when you get into the larger R chains off of the Gallate Acid, there's less absorption, right?

DR. DAVID COHEN: But there are differences in, quote, "reported sensitization."

DR. BELSITO: Yeah, but if it doesn't get through the stratum corneum, if it's not absorbed and it doesn't get to Langerhans cells, how's it causing sensitization?

DR. DAVID COHEN: Well, apparently, somehow, it is. Right? I mean, it is somehow creating positive patch test, right?

DR. BELSITO: Because it's irritating. Because it's irritating.

DR. DAVID COHEN: And, you know, the Langerhans cells may not be the whole story here. There may be other dendritic cells that are participating in sensitization.

DR. BELSITO: Yeah, dermal dendritic cells, which are even farther down.

DR. DAVID COHEN: But you can't argue the fact that people report positive patch tests to the Dodecyl Gallate, right?

DR. BELSITO: I can argue with the fact that people report garbage.

DR. DAVID COHEN: I mean, you probably are on some of those articles, Don.

DR. ROSS: Can I just go through my list? I couldn't get there to where you were with Dodecyl, and I'm just looking at the endpoints here. And if I read across the tox table, and I've got my little list here, it says for Dodecyl you would need acute tox, dermal irritation, Don -- not sensitization -- dermal irritation, ocular irritation, DART and genotox. That's a pretty long list.

And so, if you're dragging it across into the category with Propyl and clearing it, I'm not sure I can get that based on that list of needs. I don't know what others sense is.

DR. BELSITO: Well, these are esters, right? So there's going to be some hydrolysis.

DR. ROSS: Yeah.

DR. BELSITO: And so, are you concerned about the alcohols that would come off? Because if you're clearing Gallate Acid for those endpoints, then is there anything in the alcohols that you would be concerned about? I think we've already looked at them, and they're safe as used, no?

DR. ROSS: But, if you look at how the distribution of these things would be, the concentrations you would get after administration, based on those physicochemical differences, you'd expect to see huge differences, right, in pharmacokinetics and toxicokinetics.

DR. BELSITO: But the ones larger than Propyl we've already ascertained are going to be absorbed less, right?

DR. ROSS: They'd be stuck in the membrane given those logP values, yes, I think.

DR. RETTIE: I mean, we have data in the dossier that says percutaneous absorption of Caprylyl is as high as 14 percent, and that's kind of in the middle of our range. I don't believe we have numbers for the others. But 14 is not inconsequential.

DR. ROSS: Yeah, no, that's right. And maybe Curt will tell us that they're transporter substrates, but that's out of my expertise.

DR. BERGFELD: Someone had a question. I saw a hand go up. Who is that?

MS. FERGUSON: It was me. I just wanted to comment on Dr. Rettie saying that the Dodecyl log K_{ow} is incorrect. I checked the original report, and it says 3.21, but I had Bart recalculate with (inaudible) yesterday, and the log K_{ow} for that ingredient was 6.75.

DR. RETTIE: Yeah.

DR. ROSS: That's a huge difference. Yeah.

DR. BERGFELD: All right, we need to proceed. So, Dr. Cohen, this is your ingredient, what do you propose?

DR. DAVID COHEN: Yeah, it is. So, we issued an IDA for everything. We wanted ocular irritation of Propyl Gallate at relevant max use concentrations, maximum concentration of use for Caprylyl, Dodecyl and Ethylhexyl. And if eye area use is confirmed, we wanted ocular irritation data at max use.

DR. BERGFELD: It was proposed by Don that it could be non-irritating stated to the Conclusion. Would that get rid of some of that need if you did that?

DR. DAVID COHEN: Well, I don't think so. I suppose that Propyl could probably go with a safe as used when formulated to be non-irritating, with the ambiguous eye data.

DR. ROSS: I think so. I think so, David, yeah.

DR. DAVID COHEN: Yeah. So, Don, are you amenable to Propyl clearing as safe as used when formulated to be non-irritating, and have continuing insufficiencies on the others?

DR. BELSITO: I'm actually okay with all of them safe as used when formulated to be non-irritating, and that's what my team agreed to yesterday. But it sounds like some of the team members may be backing out of that conclusion, so I'll ask them.

DR. SNYDER: No, I stand by original conclusion, Don, safe when formulated to be non-irritating.

DR. BELSITO: I do, too. Allan?

DR. RETTIE: I guess I'm backing out for the Dodecyl. Spent a lot of time looking at this over the last few days. So, yep, that's where I'm at.

DR. BELSITO: So, I'm assuming that if Allan goes with your team, you're going to win the vote anyway, but why don't we call a vote?

DR. BERGFELD: Okay. So, restate your conclusion. And is someone going to second it, so we can vote?

DR. ROSS: I'll second it.

DR. BERGFELD: Okay. All right, restate your conclusion, David.

DR. DAVID COHEN: All right. So we have the motion, is Propyl Gallate is safe as used when formulated to be non-irritating. The data remain insufficient for Caprylyl, Dodecyl, Ethylhexyl. We want max use concentration for Caprylyl, Dodecyl and Ethylhexyl, and if eye area uses are confirmed for any of the newly added gallates, octal irritation at relevant maximum use concentration. And one thing I just need clarification from the team, did we want sensitization on Ethylhexyl?

DR. ROSS: Yes, I think you've got no data on the Ethylhexyl.

DR. DAVID COHEN: Yeah, and irritation sensitization on Ethylhexyl.

DR. ROSS: But, when you look across the table, there's a lot more needs for Caprylyl, Dodecyl. You know, you haven't got acute tox data, you haven't got DART data, you haven't got genotox data. If you're not reading across, you would need all of those.

DR. DAVID COHEN: Okay, let me just --

DR. SNYDER: Don, didn't we discuss about these are antioxidants in foods?

DR. BELSITO: Yeah. Well, Propyl is listed as an antioxidant in food.

DR. DAVID COHEN: But we're clearing that.

DR. KLAASSEN: Actually, I think three of them are used as antioxidants, and they are GRAS, which gives me some added confidence.

DR. ROSS: It's at a certain level.

DR. RETTIE: Is that right? Didn't we have a discussion yesterday about some of them not being GRAS?

DR. BELSITO: Yes. But we looked at it, and they are approved by the FDA for food uses.

DR. BERGFELD: All of them, or just some of them?

DR. DAVID COHEN: It says Propyl is.

DR. BELSITO: You have to go to non-cosmetic uses.

DR. ROSS: Yeah, it says Propyl.

DR. DAVID COHEN: And then, in the old report I see Propyl is listed as GRAS, but I don't see the others.

DR. BELSITO: Well, the old report was just on Propyl, David.

MS. FERGUSON: If you look at the new text, about in the middle of the paragraph, it says Caprylyl, Dodecyl and Propyl are specifically permitted for use as an antioxidant in standardized margarine levels not to exceed 0.02 of the weight of the finished food.

DR. BELSITO: Yeah.

DR. DAVID COHEN: So, Priya, which one is not?

DR. BELSITO: Ethylhexyl is not mentioned, right? It's the only one.

DR. DAVID COHEN: It's the only one we don't have much information on anything on it.

DR. BELSITO: If you're going with Caprylyl, Dodecyl, Propyl, are you worried about Ethylhexyl? I mean, how far are we going to go down this rabbit hole?

DR. DAVID COHEN: It's a legitimate pushback. So, David, could that be pulled in on those asks?

DR. ROSS: Sorry, what was the specific question?

DR. BELSITO: Are you still going to go with asks, aware that the FDA has approved them for use in foods?

DR. DAVID COHEN: We're talking about the tox stuff, right, Don?

DR. BELSITO: Yeah, but what tox are you concerned about, irritation, right?

DR. DAVID COHEN: Yeah.

DR. BELSITO: If you assume that you don't need systemic because the FDA has approved food uses, and you go ahead and say, "Safe when used when formulated to be non-irritating," haven't you cleared the tox use you're concerned about? Irritation?

DR. DAVID COHEN: What about sensitization?

DR. BELSITO: I'm not concerned about sensitization. I don't think they're sensitizers.

DR. DAVID COHEN: I think there's just too much data on it that has it. I mean, I understand your point, and it's not even that I disagree with it.

DR. BELSITO: There's data that they have positive patch test reactions.

DR. DAVID COHEN: Yes.

DR. BELSITO: I don't think there's data showing that those reactions are sensitizers.

DR. DAVID COHEN: Don, how often have we had a conversation when we dug into the sensitization data and said they haven't corroborated the relevance of that? Almost never, right? But, Don, I am acquiescing to the fact that we are mired down in our poor understanding of the relevance of these reactions. But I'm just not there to say that I --

DR. BELSITO: Well, what about formulated to be non-sensitizing and non-irritating? Because you're not going to get data on -- you know, we have the data that's out there. And if you look at the strength of those positive patch test reactions, they're all going to be questionable and one-plus. Very few are going to be two- or three-plus.

DR. DAVID COHEN: And when formulated to be non-sensitizing, have we not used that a lot for botanical products and not in this setting? Or have we?

DR. BERGFELD: Correct.

DR. BELSITO: We've used it for Cocamidopropyl betaine, we've used it for MI. We have just used it for bronopol. I mean, I don't think we need it for these ingredients. I mean, again, I think the positive responses on patch tests are irritant.

DR. DAVID COHEN: David, are you okay with your tox needs on that? Because I can get my head around non-irritating and non-sensitizing.

DR. ROSS: No, I can understand that. I've got two facts that keep bouncing back to me here. One, we're not necessarily comfortable with read-across, okay? So that's the first fact.

The second point is when I look at this tox table and I look at -- if we're not comfortable with read-across, and you look at all the data gaps we have -- and it's not just irritation and sensitization. If you look at all the data gaps we have with Caprylyl, Dodecyl, and Ethylhexyl, and there's a lot of gaps, acute tox, DART, genotox --

DR. BELSITO: But Caprylyl and Dodecyl are approved by the FDA for foods.

DR. SAM COHEN: Right.

DR. TILTON: Yeah, we did not discuss that yesterday. I didn't realize that for these other ingredients, and so that does change things for me.

DR. ROSS: And at what level are they approved? Let's have a look at that.

DR. BELSITO: Uh, in foods.

DR. ROSS: Yeah. Non-cosmetic, yeah, 0.02 percent.

DR. SAM COHEN: 0.05 -- 0.005, and 0.02.

DR. BELSITO: 0.02 in finished food.

DR. ROSS: And do we have concentrations? We don't. We only have concentrations of --

DR. BELSITO: It's also FDA-approved in drug products as an active ingredient to 0.05.

DR. ROSS: I did see that. Yeah.

DR. BELSITO: Which is going to give you much higher systemic levels eating or intravenous -- oral, I'm sorry, it's oral and topical to 0.05 -- than you're going to get putting it on the skin.

DR. ROSS: Well, that's the best argument I've heard, actually.

DR. DAVID COHEN: Yeah, I'm moved by that.

DR. ROSS: Yeah.

DR. BERGFELD: Are you going to restate your conclusion?

DR. DAVID COHEN: Yeah. This was a great conversation. I'll go with the Alkyl Gallates as safe as used when formulated to be non-sensitizing and non-irritating.

DR. BERGFELD: And that's your proposal? That is your motion?

DR. DAVID COHEN: That's my compromised proposal.

DR. BELSITO: I'll go with that because they're not sensitizing as an issue anyway. I'm fine with that.

DR. BERGFELD: Okay.

DR. DAVID COHEN: Thank you, Don.

DR. BERGFELD: Now, I'm going to end the conversation by, is there anything else that needs to be discussed, other than the irritation, sensitization and lack of tox data?

DR. BELSITO: Well, the food use and the drug use. The estrogenic effects, the doses and routes of administration were not relevant to cosmetic use, and we have a multi-generational repro that's negative. That depigmentation was not an effect on melanogenesis, but given the severity of the reaction, it was post-inflammatory in my opinion. And there was only one report, and there was a two-year carcinogenicity study that was negative. That's what I had.

DR. BERGFELD: Okay. Anything else on your side, David?

DR. DAVID COHEN: No, he covered everything.

DR. BERGFELD: Okay. All right. I'd like to call the question, if I could. All those in favor of this conclusion of safe to be non-sensitizing and irritating? Those opposed to that conclusion? Abstaining? Approved.

We're going to move on. Okay, the next is Willow-derived ingredients, Dr. Belsito.

APRIL 1983 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Dr. Schroeter's Team evaluated the newly submitted data on eye irritation, contact sensitization, and photosensitization, and recommended to the Panel that this document be returned to his Team in June once the new data and updated search of the published literature have been incorporated into the report.

JULY 1983 MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

The following conclusion of the report was unanimously approved:

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

The majority of the Panel agreed on the following Discussion Section to support its conclusion of safety:

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

Subject to minor revisions, the document will be announced as a Tentative Report for a 90-day comment period.

[Minutes for the meeting at which the Final Report was issued not available]

NOVEMBER 2003 MEETING – THIRD REVIEW/INITIAL RE-REVIEW

Dr. Marks noted that a CIR Final Report with a conclusion stating that Propyl Gallate is safe as a cosmetic ingredient at concentrations not exceeding 1% was published in 1985. After reviewing current publications on this ingredient, Dr. Marks' Team concluded that the Final Report on Propyl Gallate should not be reopened.

Dr. Belsito said that his Team determined that the Final Report on Propyl Gallate should be reopened based on its sensitization potential. After reviewing the Final Report, Dr. Belsito noted that his Team was not certain that the data suggest that 1% Propyl Gallate was sensitizing, but that 1% Propyl Gallate was not studied. He added that the re-review document submitted to the Panel contains case reports of individuals with positive patch test reactions to 0.5% Propyl Gallate.

Dr. Belsito said that a reasonable concentration limit for Propyl Gallate-induced cutaneous sensitization needs to be determined.

Dr. Bergfeld asked Dr. Andersen to summarize minutes of the Panel's deliberations on Propyl Gallate.

Dr. Andersen said that Propyl Gallate was considered for the first time in 1982, and that the Panel issued an insufficient data report in 1983, noting that more skin sensitization data were needed. Data were received in July of 1983, and a Tentative Report with the following conclusion was issued: On the basis of the available information, the Panel concludes that Propyl Gallate is safe as a cosmetic ingredient at concentrations not exceeding 1 percent.

Dr. Andersen said that there is no indication that comments on the Tentative Report were received, and, in December of 1983, a Final Report with the conclusion indicated in the preceding paragraph was issued. Dr. Andersen said that the report discussion states that there are sensitization reactions at 0.5% and 2.0%, but not at 0.1%, and goes on to say that 1.0% is alright.

Dr. Andersen added that when the report was originally done, sensitization at a concentration of 0.5% was flagged, but 1.0% was considered to be an excellent clinical margin of safety.

Dr. Belsito said that if industry wants the existing conclusion to remain, the Panel will need to receive strong data suggesting that 1.0% Propyl Gallate is not sensitizing. He noted that the Panel has reviewed data indicating that 0.5% Propyl Gallate can be sensitizing.

Dr. Snyder noted that the re-review document mentions new eye area cosmetic products containing Propyl Gallate, and that Dr. Belsito's Team determined that the old data are sufficient to address these new products.

Dr. Andersen said that the Panel's decision at this meeting would be to begin the process to consider reopening the Final Report on Propyl Gallate. He added that, at the next Panel meeting, the Panel would review a single report draft containing the old and new data on Propyl Gallate. Dr. Andersen said that CIR should obtain the original sensitization studies (i.e. the data that were submitted in response to the insufficient data request) from the ingredient file for the Panel's review.

The Panel voted unanimously in favor of beginning the process of reopening the CIR Final Report on Propyl Gallate.

Dr. Marks said that, clinically, he has not seen an epidemic of allergy to Propyl Gallate. Very few positive reactions were found after testing over a couple of years. Dr. Marks said that the reason why a problem relating to the allergenicity of Propyl Gallate has not been observed is because the cosmetic use concentrations are well below 0.5%.

JUNE 2004 MEETING – FOURTH REVIEW/DECISION TO REOPEN

Dr. Marks stated that, at the November 13-14, 2003 Panel Meeting, the Expert Panel decided that CIR should begin the process of reopening the Final Safety Assessment on Propyl Gallate. At that time, the Panel's concern related to case reports indicating positive patch test results for 0.5% Propyl Gallate, which is a lower concentration than the 1% concentration limit that is included in the Final Safety Assessment.

Dr. Marks said that his Team had proposed reopening the safety assessment, and establishing a 0.1% concentration limit for Propyl Gallate in cosmetics products.

The Panel voted unanimously in favor of formally reopening the Final Safety Assessment on Propyl Gallate.

Dr. Andersen stated that the Panel's decision means that a Scientific Literature Review will be issued, and any interested person will have the opportunity to provide further data. The next review of this report will occur at the December 2004 Panel meeting, at which time it is likely that the Panel will reach a Tentative Amended conclusion indicating that Propyl Gallate is safe for use in cosmetics at concentrations up to 0.1%.

DECEMBER 2004 MEETING – FIFTH REVIEW/ DRAFT AMENDED REPORT

Dr. Belsito recalled that, at the November 13-14, 2003 Panel meeting, the Panel voted in favor of beginning the process of reopening the CIR Final Report on Propyl Gallate and formally reopened this report in June 2004, with the publication of a new SLR. He stated that the Final Report that was published in 1985 had the following conclusion: On the basis of the available information, the Panel concludes that Propyl Gallate is safe as a cosmetic ingredient at concentrations not exceeding 1 percent.

Dr. Belsito said that, based on the available data in the current report, the highest test concentration of Propyl Gallate that did not induce sensitization is 0.1%. With this in mind, he noted that his Team concluded that Propyl Gallate is safe in cosmetic products at concentrations up to 0.1%.

Regarding the proposed concentration limit, Dr. Marks recalled Dr. Shank's comments to the effect that only 4 animals were used in the RIPT on which the 0.1% concentration limit is based and, thus, that this study is not scientifically valid. Because of this concern, Dr. Marks noted that his Team decided that human skin irritation/sensitization data on Propyl Gallate at cosmetic use concentrations are needed.

Dr. Belsito said that the reported use concentrations of Propyl Gallate are up to 0.1%, which suggest that industry has made an effort to maintain the use concentrations of this ingredient at levels that are below the 1% concentration limit that is stated in the Final Report.

Dr. Belsito noted that in patch testing the gallates, while skin irritation reactions are prevalent, the published literature does not include a large number of case reports with sensitization reactions to the gallates. Therefore, he said that based on the history of safe use, he is quite comfortable with establishing a 0.1% concentration limit for Propyl Gallate, even though the guinea pig sensitization test on 0.1% Propyl Gallate was very limited.

Dr. Shank said that the two guinea pig sensitization tests (2 animals each) on 0.1% Propyl Gallate could not serve as the basis for the proposed 0.1% concentration limit.

Dr. Slaga said that the two guinea pig sensitization tests are insignificant studies.

Dr. McEwen said that if the gallates are being tested by the North American Contact Dermatitis Group to determine their sensitization potential and positive reactions are not being found, then this means that products with these ingredients in the marketplace are safe. With this in mind, he said that whether or not additional studies are needed is based on the professional judgement of dermatologists on the Panel.

Given that the use concentration data on Propyl Gallate in the report indicate that this ingredient is used at concentrations of ≤ 0.1% in cosmetics, Dr. Belsito wanted to know if Dr. Shank would be more comfortable with a "safe as used" conclusion.

Dr. Shank said that he is bothered by the weak sensitization data on 0.1% Propyl Gallate, especially since the Panel is revising the published conclusion. He added that if the 1% concentration limit is no longer acceptable, then the Panel must be able to say that there are new data showing that this limitation is no longer appropriate.

Dr. McEwen said that the Panel does not have data showing that the 1% concentration limit is inappropriate.

Dr. Belsito said that the data included in the published Final Report seem to indicate that 0.1% and not 1% , should have been the concentration limit for Propyl Gallate. He noted that the report discussion does not contain an explanation as to why a 1%

concentration limit was established. Dr. Belsito also brought up to the Panel's attention that the inadequate guinea pig sensitization data (4 animals total) are included in the Final Report and are not new data.

Dr. Andersen said that, procedurally, the Final Report has been reopened and a Scientific Literature Review was subsequently issued. He added that if the data requested were available, the Panel's current discussion would be terminated.

Dr. McEwen suggested that rather than requesting human skin sensitization data at a test concentration of 0.1%, the request should be revised to require testing at the maximum concentration of expected use.

Dr. Andersen said that he captured the data request as human irritation and sensitization data at the concentration of use.

Dr. Bergfeld expressed concern over the lack of an incentive on the part of the cosmetics industry to provide data, in the light of the Panel's published 1.0% concentration limit. She noted that industry may only be using Propyl Gallate at concentrations of ≤ 1.0%.

Dr. McEwen said that a statement indicating that the Panel is considering lowering its concentration limit on Propyl Gallate would accompany the request for data.

Dr. Andersen said that the basis for the Panel's data request, proposed 0.1% concentration limit, and concern over the adequacy of the available data in terms of supporting this limitation will be mentioned along with the following informal data request:

1) Human skin irritation and sensitization data at concentration of use

MARCH 2005 MEETING – SIXTH REVIEW/DRAFT TENTATIVE AMENDED REPORT

Dr. Belsito stated that the Panel decided to reopen the Final Safety Assessment on Propyl Gallate at the November 13-14, 2003 Panel meeting. The Final Report on this ingredient was published with the following conclusion in 1985: On the basis of the available information, the Panel concludes that Propyl Gallate is safe as a cosmetic ingredient at concentrations not exceeding 1%. Dr. Belsito noted that the Panel thought that this conclusion was erroneous, after reviewing the Final Report along with data that have entered the published literature since the Final Report was issued.

Upon completion of its review, the Panel proposed a new conclusion, indicating that Propyl Gallate can be used in cosmetics at concentrations ≤0.1%.

Dr. Belsito's Team

•The 1% concentration limit in the original report is incorrect and there are data indicating that 0.03% is not problem. A concentration limit of 0.1% would be considered safe.

•The fact that the 0.1% concentration limit is based on a study involving only two guinea pigs is no longer a concern because the clinical experience of the Panel can also be cited.

Dr. Marks' Team

•There was concern that the proposed 0.1% concentration limit is not sound because it is based on a study involving two guinea pigs.

•The need for a Team discussion on the adverse effects of Propyl Gallate that are reported in the literature was mentioned. According to Dr. Marks, there are no multi-center studies. However, based on his experience with patch testing patients, apparently, there are not many allergic reactions to Propyl Gallate.

•Concern over the proper concentration limit for Propyl Gallate was expressed, considering that negative patch test results were reported for 0.03% Propyl Gallate, while positive patch test results were reported for 0.1% Propyl Gallate.

•Based on his experience with patch testing, Dr. Marks stated that a concentration limit of 0.1% would be appropriate for Propyl Gallate. He noted that less than 1% of his patients that were patch tested showed positive results.

•Dr. Bergfeld insisted that a disclaimer about the need for ongoing monitoring for sensitization reactions to Propyl Gallate be added to the safety assessment.

Relative to the new conclusion, Dr. Belsito said that the following statements should appear in the report discussion: While there are only four animal studies in which 0.1% Propyl Gallate was tested, this chemical has been historically used at concentrations up to 0.1%, with very little evidence of sensitization.

Dr. Slaga confirmed that Dr. Belsito's statement is based on his professional experience.

Dr. Bergfeld noted that a similar problem existed for Chlorhexidine. She said that in the discussion section of this report, the Panel stated that, because of the lack of specific data, the continued monitoring of sensitivity should be ongoing.

Dr. Andersen stated that Chlorhexidine and its various salts were flagged by the medical devices group at FDA as potentially presenting a risk of sensitization. He added that the Panel concluded that it had set the limits low enough so that it was unlikely that this would be a problem in cosmetics. However, the Panel saw the need to include this statement: Although these data did not suggest to the CIR Expert Panel a need to change the conclusion regarding the safe use of Chlorhexidine as a preservative, reports of IgE-mediated allergic reactions are considered serious. The Panel will monitor such reports to be certain that no increase in frequency is occurring.

Dr. Andersen said that that ongoing commitment to stay aware of what is happening in the clinical setting could easily be included in the discussion section of the report on Propyl Gallate, especially since it is based on professional experience.

The Panel voted unanimously in favor of issuing a Tentative Amended Final Report with the following conclusion: On the basis of the data presented in this report, the CIR Expert Panel concludes that Propyl Gallate is safe for use in cosmetic products at concentrations less than or equal to 0.1%.

SEPTEMBER 2005 MEETING – SEVENTH REVIEW/DRAFT AMENDED FINAL REPORT

Dr. Marks stated that the Panel decided to reopen the Final Report on Propyl Gallate at the November 13-14, 2003 Expert Panel meeting, and that the concern at that time was the concentration of use. The conclusion in the published Final Report reads as follows: On the basis of the available information, the Panel concludes that Propyl Gallate is safe as a cosmetic ingredient at concentrations not exceeding 1.0 percent.

Dr. Marks added that the conclusion for the Amended Final Report that is being considered today reads as follows: On the basis of the data presented in this report, the CIR Expert Panel concludes that Propyl Gallate is safe for use in cosmetic products at concentrations less than or equal to 0.1%.

Dr. Belsito noted that the boilerplate acknowledging data gaps in the frequency of use table (i.e., ingredient use frequencies reported without use concentrations, and vice versa, for product categories), created at the last Panel meeting, should be incorporated into the discussion section of each Final Report that is being considered.

The Panel voted unanimously in favor of issuing an Amended Final Report with the following conclusion: On the basis of the data presented in this report, the CIR Expert Panel concludes that Propyl Gallate is safe for use in cosmetic products at concentrations less than or equal to 0.1%.

Amended Safety Assessment of Alkyl Gallates as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: September 11, 2026
Panel Meeting Date: October 5 – 6, 2026

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Bruce A. Brod, M.D., M.H.C.I., F.A.A.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. Previous Panel member involved in this assessment: David E. Cohen, M.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., Associate Toxicologist/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	US 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
WoE	weight-of-evidence

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) reassessed the safety of Propyl Gallate and 3 additional structurally-related alkyl gallates that had not been reviewed, as used in cosmetics. 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 August 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.

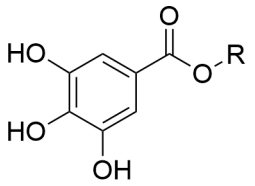


Figure 1. Alkyl gallates, wherein R is a caprylyl, dodecyl, 2-ethylhexyl, or propyl group.

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 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.

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.

Following the passage of MoCRA, the FDA created a number of new product categories including, "(17) Other preparations (i.e., those preparations that do not fit another category)" (Category 17). CIR and the Panel utilize these product categories to inform, in part, the weight-of-evidence (WoE) in exposure and risk analyses. However, citation of Category 17, alone, as the product use category is uninformative. When a product is co-categorized with both Category 17 and one or more common product use categories (e.g., eye makeup preparations), or other information in the RLD such as the product name are indicative of use type (e.g., "lip balm" is part of the product name), then those uses are accounted for and may be considered to be part of the "the present practices of use" for those products; as such, the Panel's safety conclusion may be inclusive thereon. Conversely, for instances wherein the use of an ingredient in a cosmetic product is only categorized as Category 17 and other information in the RLD is not indicative of use type, the present practices of use for these products remain unknown and the Panel's safety assessment conclusion, therefore, does not apply thereon.

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 oral exposure to 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 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 embryo yolk sacs 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]

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.*

GENOTOXICITY STUDIES

Some genotoxicity assays are no longer considered appropriate as standard methods for evaluating genotoxic potential under current OECD guidance. (See https://www.cir-safety.org/cir-findings for the identification of such study types.) Although these assays (as identified in the guidance) may be reported in the published literature, unpublished reports,

or data submissions, the results from these assays are of limited interpretability and therefore the studies are not summarized herein. [2,33,34]

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.[2] In chromosomal aberration assays, Propyl Gallate did not induce chromosomal aberrations 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 in cytogenetic and dominant lethal assays, including both in vitro (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).

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.[35-37] Caprylyl Gallate was negative in chromosomal aberration and micronucleus-based assays at concentrations ≤ 0.5 µg/ml (all assays performed without metabolic activation).[33] Propyl Gallate produced positive results in multiple mammalian cell systems including 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.[34,35,38] 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).[34,35,38,39] 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).[4,34,35,38-41]

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 of rats 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 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]

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 was characterized by tubular degeneration and regeneration, increased urinary neutrophil gelatinase-associated lipocalin, and 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. For Propyl Gallate, 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 petrolatum 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.[65-80] 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).[81] 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 test 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.[73,82-93] 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.[94] 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.

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. Oral exposure 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). Dose-dependent malformations, delayed hatching, and increased oxidative stress and apoptosis were observed following zebrafish embryo yolk injection with 1 – 50 ppm Propyl Gallate. Propyl Gallate (50 mg/kg) resulted in dysregulated mRNA expression of genes associated with various functions in the testis when evaluated in mice administered the test substance 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 was negative 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.

The Panel considered the irritation and sensitization potential of the alkyl gallates. Several positive patch test reactions have been reported; however, the Panel noted that the clinical relevance of these reactions is uncertain and that some may represent irritant, rather than sensitization responses. The Panel also considered the available irritation data, including evidence of ocular irritation, and noted limitations in the data available at concentrations relevant to cosmetic use. Accordingly, the Panel specified that products containing these alkyl gallates must be 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.

Additionally, at least 1 use for the ingredients reviewed in this assessment is reported in the RLD under Category 17, "other preparations." For instances wherein the use of an ingredient in a cosmetic product is only categorized as Category 17, and other information in the RLD is not indicative of use type, the present practices of use for such products remain unknown and the Panel's safety assessment conclusion, therefore, does not apply thereon.

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

**No concentration of use reported. For ingredients with reported uses but no reported concentration of use, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

TABLES

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

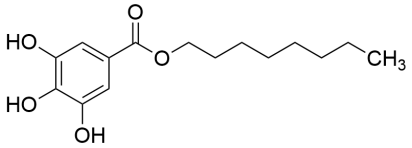
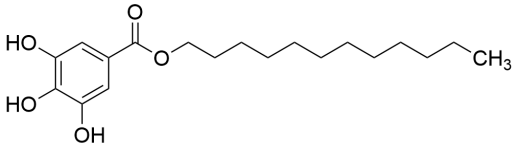
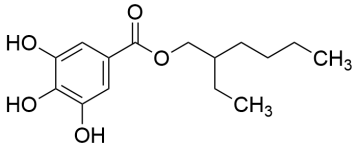
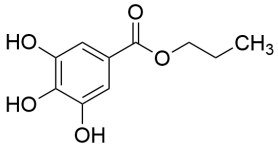
Ingredient/CAS No.	Definition	Function(s)
Caprylyl Gallate [CAS No. 1034-01-1]	Caprylyl Gallate is the organic compound that conforms to the structure: 	Antioxidant
Dodecyl Gallate [CAS No. 1166-52-5]	Dodecyl Gallate is the ester of gallic acid that conforms to the structure: 	Antioxidant
Ethylhexyl 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 (mm Hg @ 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	95
Vapor Density (mm Hg)	7.3	95
Melting Point (ºC)	146 - 150	2
Water Solubility (g/l @ 25º C)	3.49	95
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	95
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/sampling time)	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	yolk sac of 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	[35]
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	[36]
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	[37]
Chromosomal Damage						
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	negative for chromosomal damage; controls gave expected results	[33]
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	negative for chromosomal damage; no statistically-significant increases in micronuclei, nucleoplasmic bridges, or nuclear buds compared to solvent control; nuclear division index unchanged	[33]
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	negative for chromosomal damage; no statistically-significant increase in centromere-positive or centromere-negative micronuclei compared to solvent control	[33]
Propyl Gallate	saline	up to 40 µg/ml	Chinese hamster lung fibroblasts	chromosomal aberration assay; performed without metabolic activation; appropriate negative control used	positive for chromosomal damage; controls gave expected results	[35]

Table 7. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
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	positive for chromosomal damage; 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	[34]
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	positive for micronucleus induction; 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	positive for micronucleus induction; 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	positive for micronucleus induction; 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	negative for micronucleus induction; 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	positive for micronucleus induction; 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]
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 2; 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	[33]

Table 7. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
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	negative for micronucleus induction; 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)	negative for micronucleus induction; 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]
Propyl Gallate	olive oil	0 and 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; 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]
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	petrolatum	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	petrolatum	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	petrolatum	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 petrolatum	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 petrolatum	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]
Caprylyl Gallate and Dodecyl Gallate	4438 patients with allergic contact dermatitis (788 with hand eczema, 3650 without hand eczema)	2018 - 2023	retrospective study; patch testing with Chinese allergen series including Caprylyl Gallate (0.25% in petrolatum) and Dodecyl Gallate (0.25% in petrolatum); 48-h occlusive patch tests	positive responses to Caprylyl Gallate in patients with hand eczema: 60 patients (7.6% of patients) positive responses to Caprylyl Gallate in patients without hand eczema: 229 patients (6.3% of patients) positive responses to Dodecyl Gallate in patients with hand eczema: 169 patients (21.5% of patients) positive responses to Dodecyl Gallate in patients without hand eczema: 644 patients (17.6% of patients)	[80]

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 petrolatum)	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 petrolatum	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 petrolatum	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 petrolatum	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 petrolatum); 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 petrolatum	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 petrolatum	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 petrolatum	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% Propyl 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 petrolatum	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 petrolatum	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 petrolatum	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 petrolatum	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 petrolatum	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 petrolatum; 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 petrolatum	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 petrolatum) yielded positive results -additional tests with other gallates (Dodecyl Gallate (0.3% in petrolatum) and Propyl Gallate (0.5% in petrolatum) were negative -patient completely recovered after stopping lipstick use	83
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 petrolatum) and 0.3% Dodecyl Gallate (in petrolatum) -marked reduction in episodes after avoiding foods and lip preparations containing gallates	84
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	85
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	86
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 petrolatum); 48-h occlusive patches -patient had positive response to lipstick (containing Propyl Gallate but no propylene glycol), and to Propyl Gallate	87
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 petrolatum), and Propyl Gallate (1% in petrolatum) -it was discovered that the fish food containing Propyl Gallate; symptoms improved gradually after handling fish food with gloves	88
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 petrolatum) 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	89

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	90
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 petrolatum 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	91
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	82
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 petrolatum) -strong positive reaction to Dodecyl Gallate -complete recovery after abstaining from cheese counter work and brief therapy with clobetasol propionate	92
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 petrolatum) 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	93

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2

Final Report on the Safety Assessment of Propyl Gallate

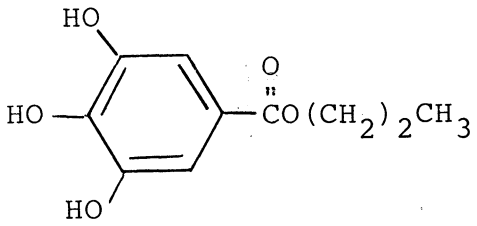
Propyl Gallate acid is used as an antioxidant in cosmetic products at concentrations normally less than 0.1 percent. Propyl Gallate is absorbed when ingested, methylated, conjugated, and excreted in the urine. Acute animal toxicity studies indicate that Propyl Gallate is slightly toxic when ingested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

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

CHEMISTRY

Description and Preparation

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



Other names for this ingredient include[2]:

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

PG
Progallin P
Tenox PG

Propyl Gallate is produced commercially by the esterification of gallic acid (trihydroxybenzoic acid) with propyl alcohol.[3]

Properties

Propyl Gallate is a fine white to light brown crystalline powder with no odor and a slightly bitter taste. It is soluble in ethanol, ethyl ether, oil, and lard but is only slightly soluble in water.[2,4,5] Propyl Gallate is also soluble in aqueous solutions of PEG ethers of cetyl alcohol; solubility increases as the concentration of the surfactant increases and the PEG chain length increases.[6] Table 1 summarizes other physical and chemical properties of Propyl Gallate.

Analytical Methods

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

TABLE 1. Physical and Chemical Properties

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

*Increasing Propyl Gallate concentration broadens curve to 290–320 nm. At 10 percent, absorption peak is greater than 390 nm.
†No information is available on organic impurities.

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TABLE 2. Analytical Methods Used in Propyl Gallate Determination

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

Reactivity

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

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

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

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

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

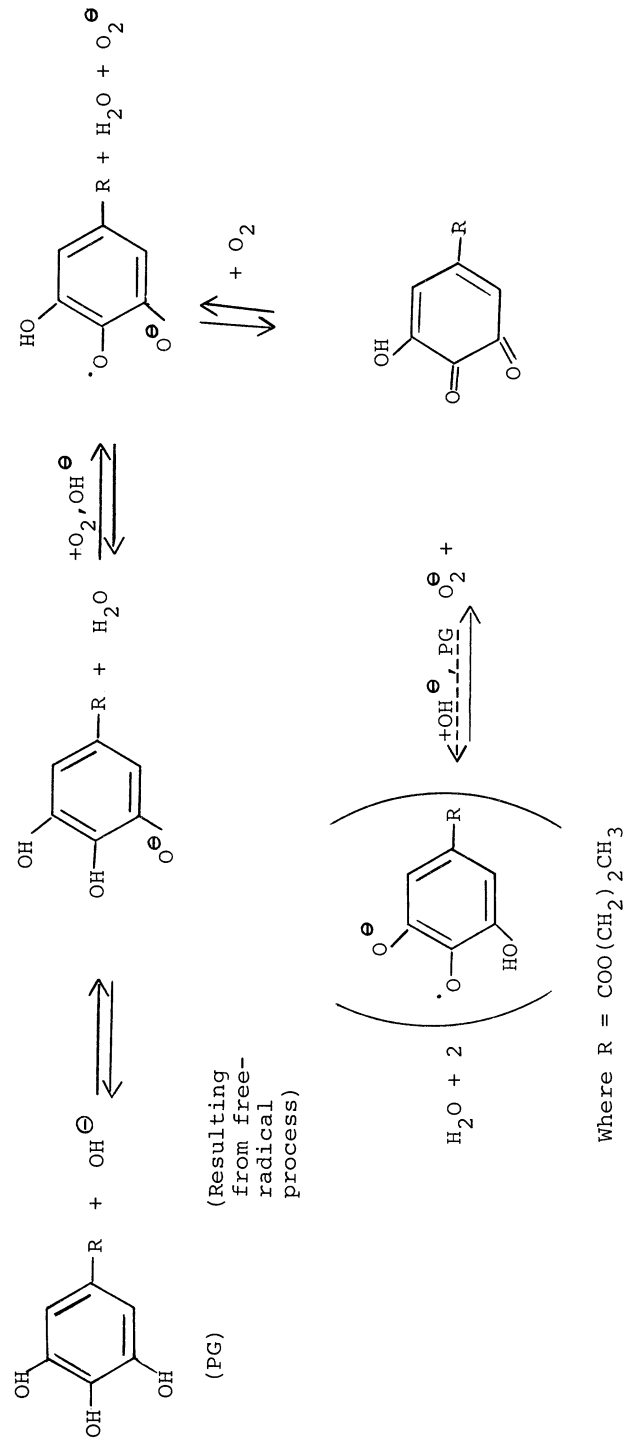


FIG. 1. Reactivity of Propyl Gallate.

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

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

USE

Cosmetic

Propyl Gallate is used as an antioxidant in cosmetics to stabilize vitamins, essential oils, perfume, as well as fats and oils, all of which readily undergo oxidation. Oxidation of these products results in rancidity, color changes, viscosity changes, and active ingredient deterioration. Oxidation can occur due to the presence of heat, light, moisture, oxygen, chemical pro-oxidants, or microorganisms. Propyl Gallate acts by inhibiting the accumulation of damaging free radicals. Propyl Gallate may be used alone but is often used in a mixture of phenolic antioxidants. BHA and Propyl Gallate are synergistic antioxidants.[37]

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

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

Food

Propyl Gallate has been employed as an antioxidant in foods since 1948 to protect fats, oils, and fat-containing food from rancidity, which results from the formation of peroxides. To some extent, it is used in essential oils to retard the oxidation of monoterpenes and oxidation-sensitive aldehydes and ketones. The sol-

TABLE 3. Product Formulation Data[38]

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

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ubility of Propyl Gallate in fats and oils is limited to less than 2 percent. Propyl Gallate is often difficult to dissolve in these substances without the aid of a carrier solvent.[35,36,40]

Propyl Gallate is used at concentrations of 0.01484 to 0.00001 percent in fats and oils, meat products, snack foods, baked goods, nut products, grain products, frostings, chewing gum, soft candy, frozen dairy products, gelatin products, and alcoholic and nonalcoholic beverages. The FDA has placed the limit on the total antioxidant content of food at 0.02 percent of the fat or oil content of the food.[40]

A National Research Council Subcommittee has estimated the average daily intake of Propyl Gallate from foods to be 0.014 mg/kg for ages 0 to 5 months, 0.114 mg/kg for ages 6 to 11 months, 0.135 mg/kg for ages 12 to 23 months, and 0.065 mg/kg for ages 2 to 65+ years. The Select Committee of the LSRO[40] concluded that these figures accurately reflect the actual amounts of Propyl Gallate consumed by these various groups.

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

Propyl Gallate is used as a direct food additive in 12 European countries, as well as Canada, Australia, South Africa, and Russia at concentrations up to 2.0 percent.[41]

BIOLOGICAL EFFECTS

Antimicrobial Activity

Jordan et al.[42] studied the antibacterial effects of Propyl Gallate on bacteria of the human oral cavity. At concentrations of 0.0032 to 0.266 percent, Propyl Gallate inhibited the growth of 27 strains of bacteria. The authors considered this effect significant in regard to the ability of Propyl Gallate to inhibit cariogenesis. Against *Salmonella narasino* and *Saccharomyces cerevisiae*, Gallate esters were bactericidal; the effect increased as the alkyl chain length increased.[43] Shih and Harris[44] observed Propyl Gallate, at 400 ppm, to be lethal to *Escherichia coli*, but it had little effect at this concentration on *Staphylococcus aureus*. They also observed that combinations of butylated hydroxyanisole (BHA) and Propyl Gallate were more effective than either ingredient alone, indicating a synergistic effect. They concluded, however, that at the concentrations used in foods, Propyl Gallate probably has low antimicrobial activity.

The effect of Propyl Gallate on *E. coli* was further studied in 1979 by Boyd and Beveridge. The antibacterial activity of this ingredient was positively correlated with its solubility, partition coefficient, pKa, and reduction of water surface tension. The authors suggested that Propyl Gallate exerts antibacterial activity by interfering with some biochemical free radical intermediate within the organism. The action was not due to uncoupling of the bacteria's oxidative phosphorylation system or damage to the cytoplasmic membrane. Propyl Gallate did inhibit respiration and malate dehydrogenase activity and altered the cytochrome spectra of

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treated cells, suggesting interference with the terminal cytochrome system. Propyl Gallate also inhibited synthesis of the general cell polymers, RNA, DNA, and protein.

Propyl Gallate stabilizes oxidation-sensitive amphotericin-B and prolongs its antifungal activity. An antifungal synergism between these two compounds has been suggested.[45,46]

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

Biochemical Reactions

Propyl Gallate inhibited eosin-sensitized photodynamic oxidation of trypsin by competing efficiently with oxygen and trypsin for reaction with the eosin triplet (excited) state. Propyl Gallate reduced the excited eosin to form a semireduced eosin radical and an oxidized Propyl Gallate form. Then, by reverse electron transfer, ground state eosin and Propyl Gallate were regenerated. Photodynamic activation occurred with the formation of a free radical, and Propyl Gallate acted by inhibiting free-radical formation.[48]

Propyl Gallate also inhibited mild oxidation of serum low-density lipoprotein. Upon oxidation, the apoprotein was converted from a homogeneous, high-weight substance to a mixture of low-weight polypeptides. This resulted from a reaction between the protein moiety and the autooxidizing lipid moiety of the lipoprotein. Addition of Propyl Gallate to the serum inhibited this reaction.[49]

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

Inhibition of Formation of Carcinogenic Nitrosamines

Kawanishi et al.[51] found that Propyl Gallate inhibited nitrosamine formation from aminopyrine and sodium nitrite in rat stomachs. Inhibition was as high as 55 percent at a dose of 100 μmol Propyl Gallate per kg body weight; Propyl Gallate was considered a relatively strong inhibitor. Similarly, Rao et al.[52] observed that Propyl Gallate inhibited nitrosamine formation in human saliva from the interaction of salivary nitrite with aminopyrine and oxytetracycline by acting as a nitrite scavenger. Inhibition produced by 10 mM Propyl Gallate ranged from 42 to 53 percent at pH 3.

Effects on Enzymes and Enzyme Systems

Free radicals are generated at almost all stages of glycolysis, respiration, oxidation, and certain enzyme systems, among other biochemical processes. Since Propyl Gallate is a free-radical inhibitor, it would be expected to affect all of these systems. Propyl Gallate decreased the activity of certain redox enzymes, such as D-glyceraldehyde-3-phosphate dehydrogenase, lactic dehydrogenase, and alcohol dehydrogenase, all of which produce free-radical intermediates; it did not inhibit aldolase and enolase, which produce no free radicals.[53] Vartanyan et al.[54] observed the inactivation of lactic dehydrogenase by Propyl Gallate was due to the oxidation of sulfhydryl (SH) groups of the enzyme by Propyl Gallate

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radicals (7.1×10^{-4} M). Brzhevskaya et al.[55] reported that Propyl Gallate, at concentrations of 1×10^{-3} M to 6.7×10^{-3} M, inhibited the enzymatic hydrolysis of adenosine triphosphate (ATP) 40 to 85 percent by blocking the formation of free radicals. Agatova and Emanuel[56] stated that radicals of Propyl Gallate (at concentration of 1×10^{-3} M) accelerated the conversion of SH groups of enzymes to S–S bonds under oxidation. Both the formation of S–S bonds and the destruction of SH bonds deactivate enzymes. They observed that D-glyceraldehyde-3-phosphate dehydrogenase, which contains SH groups, was affected, whereas RNA-ase and trypsin, with S–S bonds but no SH bonds, were not affected.

Propyl Gallate significantly inhibited tyrosine hydroxylase activity in vitro at concentrations of 10^{-4} to 10^{-6} M but was noninhibiting to tyrosine hydroxylase in vivo when administered intraperitoneally at 200 or 400 mg/kg in guinea pigs.[57]

Propyl Gallate inhibited microsomal aminopyrine demethylase (part of the microsomal mixed-function oxidase system) and NADPH-cytochrome c reductase activities. Propyl Gallate readily reacted with radical species of these systems and strongly inhibited NADPH-dependent lipid peroxidation in microsomes.[58] Yang and Strickhart[59] observed that Propyl Gallate inhibited microsomal benzo[a]pyrene hydroxylase and demethylase activities in vivo, with 50 percent inhibition occurring at 50 and 140 to 500 μM Propyl Gallate, respectively. Propyl Gallate did not, however, inhibit NADPH-dependent reduction of cytochrome P-450, indicating that the site of inhibition was not on NADPH-cytochrome c reductase, as Torrielli and Slater[58] had suggested. The authors believed the site of inhibition was cytochrome P-450 itself. In 1977, Rahimtula et al.[60] confirmed that Propyl Gallate (25 to 125 μM) did not inhibit NADPH-cytochrome P-450 reductase but did inhibit benzo[a]pyrene hydroxylase.

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

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

Propyl Gallate, which is metabolized to a substrate for Phase II xenobiotic metabolizing enzymes (glucuronide formation) in the liver, was injected intraperitoneally into rats daily for 7 days at a dose of 150 mg/kg per day. Animals were then killed, and homogenates obtained from the liver were analyzed for enzymic activity. Urine was analyzed daily during treatment for the presence of metabolites of D-glucuronic acid. Propyl Gallate had no effect on hepatic Phase I xenobiotic metabolism (mixed-function oxidase system), cytochrome P-450, or microsomal protein content. Propyl Gallate did stimulate hepatic microsomal UDP-glucuronyltransferase activity and increased excretion of free and conjugated D-glucuronic acid.[66]

The effect of Propyl Gallate on the hepatic mixed-function oxidase system was studied in weanling rats. Animals were placed on diets containing various amounts and types of fat plus 0 or 0.3 percent Propyl Gallate for 50 days. Rats were then killed, the livers were removed, and homogenates were prepared and

assayed. Rats on diets containing Propyl Gallate had no significant differences in average body weights, liver weights, liver:body weight ratios, or in microsomal protein content in comparison to controls. Two hepatic microsomal mixed-function oxidases, aniline hydroxylase and amino pyrine N-demethylase, were unaffected by Propyl Gallate. Propyl Gallate also had no effect on cytochrome P-450 content or NADPH-cytochrome c reductase activity. Propyl Gallate appeared to have no in vivo influence on the rat hepatic microsomal metabolizing system.

Endocrinological Effects

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

Beetens and Herman[70] observed that Propyl Gallate enhanced the formation of 6-oxo-$PGF_{1\alpha}$ by incubation with ram seminal vesicle microsomes. This resulted either from stimulation of prostacyclin synthetase or from inhibition of a prostacyclin synthetase inhibitor.

Propyl Gallate inhibited arachidonic acid-induced serum platelet aggregation by inhibiting serum platelet microsomal prostaglandin synthetase. Propyl Gallate did not inhibit ADP-induced platelet aggregation.[69]

The effect of Propyl Gallate on prostaglandin synthetase activity of mammary gland tissue was studied in vivo. Female Sprague-Dawley rats were fed diets containing various lipid content, with or without Propyl Gallate (0.3 percent). Rats were killed 24 hours later, and homogenates of mammary gland tissues were prepared for prostaglandin synthetase determination. Dietary Propyl Gallate produced an elevation of $PGF_{2\alpha}$ but had no effect on PGE_2. It was suggested that Propyl Gallate scavenged the oxygen radical formed during the conversion of PGG_2 to PGH_2 and, consequently, altered the amount and types of prostaglandins produced by the mammary gland.[71]

Propyl Gallate altered prostaglandin endoperoxide synthetase and peroxidase activities of seminal vesicle microsomes. At 0.1 mM Propyl Gallate, production of $PGF_{2\alpha}$ and PGE_2 by mammary gland tissue microsomes was stimulated, but at higher concentrations (0.50 to 2.50 mM) inhibition occurred. Mammary gland tissue microsomes of rats fed diets containing 0.3 percent Propyl Gallate synthesized more $PGF_{2\alpha}$ and PGI_2 than did controls. Exogenous Propyl Gallate stimulated production of $PGF_{2\alpha}$ and PGE_2 in rats fed control diets and rats fed vitamin E-deficient diets. The author concluded that Propyl Gallate had a concentration-dependent effect on the biosynthesis of prostaglandins by regulating the availability of lipid peroxide intermediate.[72]

Cellular/Tissue Effects

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

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

The effect of Propyl Gallate on mouse lung metabolism was studied by Omaye et al.[75] Groups of 16 to 24 adult mice were given single intraperitoneal injections of 0, 50, 100, or 200 mg/kg Propyl Gallate. Three days later, mice were killed, and the lungs were examined for lesions, weighed, and assayed for enzyme activity as well as DNA content. No significant pulmonary abnormalities or biochemical changes were observed in mice injected with up to 200 mg/kg Propyl Gallate.

Neurological/Neuromuscular Effects

The effect of gallates on bradykinin-induced smooth muscle contraction was studied in the isolated guinea pig ileum. When Propyl Gallate was mixed with bradykinin (a vasoactive peptide), the contractile response was suppressed. Length of the gallate alkyl side-chain influenced the degree of inhibition. The results indicated that Propyl Gallate (10^{-4} M) was a strong, partially competitive inhibitor of bradykinin; the inhibition was moderately reversible.[76]

Modak and Rao[77] studied the anesthetic activity of Propyl Gallate. Propyl Gallate was an effective anesthetic on the lumbar plexus of frogs. Infiltration anesthesia was studied in groups of 8 rabbits and guinea pigs. Propyl Gallate (1 percent in saline) was injected intradermally into the epilated skin of each animal. Procaine HCl was injected in other sites of the same animal to compare the response to Propyl Gallate. Pinprick reaction in these injection sites was recorded along with adverse reactions to drug injection. Onset and duration of anesthesia were also recorded. Potentiation of Propyl Gallate's anesthetic activity by epinephrine was studied as above in each of 4 rabbits. Results of these tests indicated that Propyl Gallate possessed good local anesthetic activity when compared to a known anesthetic (Procaine). The activity of Propyl Gallate in infiltration anesthesia was potentiated by epinephrine.

The effect of Propyl Gallate on arachidonic acid (AA)-induced abdominal contractions was studied in mice. Treatment consisted of intraperitoneal injection, subcutaneous injection, or oral ingestion of an AA-Propyl Gallate mixture, Propyl Gallate then AA, AA then Propyl Gallate, or AA and Propyl Gallate simultaneously. Positive and negative controls were included in this study. Propyl Gallate inhibited AA-induced contractions when administered intraperitoneally as a mixture with AA (2 mg/ml incubate), as a pretreatment (4 mg/kg), or simultaneously with AA (100 μg/ml incubate). Oral and subcutaneous administration of 10 or 40 mg/kg Propyl Gallate had no effect on AA-induced contractions. The antinociceptive effect of Propyl Gallate may be due in part to its anesthetic effect and in part to deactivation of arachidonic acid.[68]

Special Studies

Ionizing/Ultraviolet Radiation Protection

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

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

It was determined that Propyl Gallate inhibited DNA depolymerization induced by ionizing radiation in vitro.[79-82] Pre- or posttreatment with Propyl Gallate increased the survival rate of monkey heart cells in vitro following gamma-radiation.[83] Sheng et al.[84] found radiation-induced spins could be transferred from DNA to Propyl Gallate and believed it was exclusively due to a hydrogen transfer mechanism.

Propyl Gallate inhibited lipid peroxidation in lysosomal membranes treated with high-energy radiation in vitro.[85] This result prompted Kahn et al.[8] to study the photoprotective effect of Propyl Gallate in two in vitro systems, photohemolysis of red blood cells (RBCs) and growth inhibition of *Candida albicans* by light. Propyl Gallate protected RBCs from ultraviolet light (280 to 370 nm) via energy absorption and significantly reduced the oxygen tension of the system (photohemolysis is inhibited by decreased oxygen tension). Propyl Gallate did not protect *C. albicans* from the deleterious effects of radiation. As a photoprotector, Propyl Gallate may act by reducing the formation of free radicals during radiolysis of tissue water, which react with membrane lipids to produce damaging lipoperoxides, or it may act as a free-radical scavenger to neutralize free radicals formed by hydrogen donation.

Propyl Gallate (0.3 to 1 mg/ml) protected *Salmonella typhimurium* against the lethal and mutagenic effects of gamma-radiation in the presence of oxygen. The magnitude of protection in each case was similar. No protection occurred when Propyl Gallate was added immediately after radiation.[86]

The effect of Propyl Gallate as an ultraviolet light protector was studied in vivo by McDonald-Gibson and Schneider.[87] The test material (up to 10 percent w/w) was applied to the epilated ear of guinea pigs either before or after UV radiation. In unprotected sites, radiation resulted in erythema, edema and blister formation. Pretreatment with Propyl Gallate inhibited induction of erythema, edema, and pyresis. Posttreatment inhibited blister formation. In a similar study, Propyl Gallate (3 to 15 mg/animal) was applied under occlusion to male rat epilated dorsal skin immediately after radiation with a Hanovia Model 10 quartz lamp (with filter) emitting UV light greater than 295 nm. Erythema was assessed 4 hours later. When compared to control sites, Propyl Gallate reduced UV light-induced erythema. This effect may be linked to its inhibition of prostaglandin synthesis.[88]

Chemoprotection

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

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Antimutagenesis

Propyl Gallate inhibited the mutagenic activity of dimethylnitrosamine in a DNA-repair test. They suggested that antioxidants may act as antimutagens by preventing the formation of reactive carcinogens or by competing with proximate carcinogens or mutagens.[98] In two studies, Propyl Gallate (25 to 125 μM and 410 nmol/plate) inhibited the mutagenic activity of benzo[a]pyrene (BP) metabolites in *S. typhimurium* strain TA98.[60,99] Rahimtula et al.[60] claimed that Propyl Gallate inhibited BP-hydroxylase in the microsomal preparation. Springarn and Garvie[100] reported that Propyl Gallate inhibited the formation of mutagenic pyrazine derivatives in sugar–ammonia systems when assayed in *S. typhimurium* TA98 and TA100 in the presence and absence of rat hepatic microsomes. In another study, Propyl Gallate inhibited the mutagenicity of N-methyl-N'-nitro-N-nitrosoguanidine and N-acetoxy-2-acetyl-aminofluorine in the same test organisms.[101] Propyl Gallate also reduced the mutagenic activity of pyrolysis products of albumin (0.2 g Propyl Gallate to 1 g albumin) in Ames assays using *S. typhimurium* TA98.[102] In addition, Propyl Gallate reduced the mutagenic activity of aflatoxin B_1 in *S. typhimurium* TA98 under metabolic activation,[103] but in a similar study, it slightly increased (by 50 to 100 percent at highest dose tested) the mutagenic effect of this carcinogen in *S. typhimurium* TA100.[104]

Anticarcinogenesis/Antitumorigenesis

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

McCay et al.[106] observed that Propyl Gallate protected rats against the induction of tumors by dimethylbenzanthracene (DMBA). Six groups of 30 weanling rats were placed on diets containing polyunsaturated fat, saturated fat, or no fat, with or without addition of 0.3 percent Propyl Gallate. Fifty days later, half of each group were given 10 mg DMBA orally. Six months later, all rats were killed and examined for tumors. The results indicated that Propyl Gallate inhibited DMBA-induced tumorigenesis; however, both the amount of fat and degree of unsaturation affected the extent of inhibition.

Anticancer

Emanuel et al.[107] reported that Propyl Gallate inhibited the activity of important oxidation–reduction enzymes necessary for the intensive biosynthetic processes of tumor cells in vitro. Further, Propyl Gallate (0.01 to 0.75 percent) selectively reduced the RNA content of tumor cells without significantly affecting the RNA content of normal, noncancerous cells. Tumor cells treated with this ingredient also lost their implantability into host animals. Lipchina et al.[108] observed that Propyl Gallate (0.15 mg/ml) suppressed mitosis in Hela tumor cells; its selectivity for tumor cells was dependent upon concentration and time of exposure. Propyl Gallate also significantly increased the number of chromosome

aberrations and altered the metabolic activity of tumor cells. These authors concluded that Propyl Gallate's selectivity may be due to a difference in the content of natural inhibitors between tumor and normal cells.

In 1961, Emanuel stated that Propyl Gallate can act specifically to suppress glycolysis, as well as the activities of cytochrome oxidase and many dehydrogenases. Kukushkina et al.[109,110] reported that Propyl Gallate inhibited protein and nucleic acid biosynthesis in Erhlich ascites carcinomas and solid hepatomas, whereas in vivo it did not affect these biosynthetic processes in healthy tissue. Furthermore, Propyl Gallate inhibited these processes in cultured human laryngeal cancer cells. Emanuel et al.[111] reported that Propyl Gallate inhibited RNA formation in Ehrlich ascites carcinoma cell preparations. This effect probably was due to the interaction of Propyl Gallate with the SH groups of enzymes involved with RNA transcription.

Propyl Gallate has been shown to have either a radioprotective or a radiosensitizing effect, depending on the duration of its action before radiation. Aphanasjev et al.[112] first reported the radiosensitizing effect of Propyl Gallate on tumors. Multiple intraperitoneal injections of this ingredient enhanced the lethal action of local ionizing radiation for lymphosarcomas in mice. More Propyl Gallate-treated mice had regressing tumors than those receiving radiation alone; additionally, the growth of nonregressing tumors decreased in these test animals. Odintsova and Kruglyakova,[113] in experiments with isolated DNA, reported that the radioprotective effect of Propyl Gallate increased as the concentration of unoxidized Propyl Gallate (maximum effect at 1.65×10^{-2} M) increased before radiation and likewise the radioprotective effect decreased as the time of pre-irradiation exposure to unoxidized and oxidized Propyl Gallate increased. This latter decrease in the radioprotective effect can, in some cases, result in radiosensitization; initial injury to DNA by Propyl Gallate before radiation enhances the injurious effects of radiation.

Antiteratogenesis

Propyl Gallate inhibition of teratogenesis by certain chemicals has been studied. When fed to vitamin E-deficient pregnant rats, Propyl Gallate prevented the teratogenic effects of the vitamin deficiency, as the incidence of congenital abnormalities and resorptions was reduced. Propyl Gallate was added to the diet at concentrations of 0 to 0.4 percent along with doses of 0 to 10 mg/rat vitamin E. On the twenty-first day of gestation, the rats were killed and the fetuses were examined. At 0.025 percent, Propyl Gallate did not reduce the frequency of vitamin E deficiency-induced malformations; at 0.4 percent alone or at lower concentrations with vitamin E supplements, Propyl Gallate reduced the teratogenic effects.[114]

Desesso[115] studied the effect of Propyl Gallate on hydroxyurea (HU)-induced teratogenesis. Various amounts of Propyl Gallate (362–906 mg/kg) and HU were injected simultaneously into rabbits or administered as a mixed solution on the twelfth gestational day. The highest dose of Propyl Gallate (906 mg/kg) was toxic to the pregnant animals, although increasing amounts of Propyl Gallate inhibited the effects of HU in a dose–response relationship. Propyl Gallate reduced the number of malformed fetuses and resorptions, the severity of anomalies, and the range of HU-induced defects. The mixed solution of Propyl Gallate and HU was more efficacious than simultaneous injection of the com-

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pounds. However, data obtained by thin-layer chromatography indicated that the two compounds do not react chemically. The length of time the mixed solution was allowed to stand prior to injection also had no effect on the results. Desesso suggested that the antioxidant properties of Propyl Gallate acted within the embryo to reduce the severity of HU teratogenesis.

Anticariogenesis

In the 1960s, the effect of Propyl Gallate on caries was studied extensively. Jordan et al.[42] placed rats on cariogenic diets with and without 0.5 percent Propyl Gallate for 90 days. Animals were then killed, and molar teeth were scored for number of caries. Positive and negative controls were included in the study. Propyl Gallate significantly reduced the number of caries per rat. At this concentration, Propyl Gallate resulted in reduced weight gains but no excessive mortality. Characteristic brown stains were observed on the surface layers of the dentin of rats on the Propyl Gallate diet; this effect was supposedly due to the formation of metal-gallate precipitates from the diet. Thus, Propyl Gallate acts as an antibacterial agent in reducing caries.

Lisanti and Eichel[116] studied the cariogenic effect in hamsters. Groups of 40 animals were fed control or cariogenic diets, which included 0 or 0.03 percent Propyl Gallate in the drinking water for 50 days. Animals were then killed, and teeth were scored for caries. Animals on the Propyl Gallate diet had significant weight reductions. Propyl Gallate reduced the number of caries when compared to positive and negative controls. Total number of caries was reduced by 60 percent in male rats and by 36 percent in female rats. Therefore, a metabolic tooth defect in this strain of animals, induced by a cariogenic diet, was partially corrected by ingestion of Propyl Gallate.

Thompson et al.[117] reported the results of a 30-day study of Propyl Gallate in cotton rats. Groups of 16 animals were fed a cariogenic diet containing 0.5 percent Propyl Gallate for 30 days. Rats were then killed, and teeth were scored for caries. Propyl Gallate did not induce significant weight reduction in animals; it also did not reduce the incidence of caries. Propyl Gallate-fed rats had a significantly higher incidence of caries when compared to controls.

Absorption, Metabolism, and Excretion

Orten et al.[118] analyzed the urine from dogs fed diets containing 0.0117 percent Propyl Gallate for 14 months. During this time, no detectable quantities of Propyl Gallate were found in the urine. Van Esch[119] studied the in vivo and in vitro metabolism of Propyl Gallate. He determined that pancreatic extracts containing lipases and esterases did not hydrolyze Propyl Gallate, indicating that it was not hydrolyzed in the gut. Blood esterases also did not hydrolyze Propyl Gallate. When fed to rats, most of the Propyl Gallate was passed in the feces as the original ester. The urinary components detected were the original ester and gallic acid, and these were excreted completely within 24 hours.

Dacre[120] and Booth et al.[121] studied extensively the metabolism and excretion of Propyl Gallate in rats and rabbits. When Propyl Gallate was administered orally to rats, the major urinary metabolite was 4-methoxygallic acid, whereas 2-methoxypyrogallol, gallic acid, and glucuronides of the methoxylated products were the minor metabolites. When Propyl Gallate was given orally to rabbits, 79

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

ANIMAL TOXICOLOGY

Acute Effects

Oral Toxicity

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

Three lipstick formulations were evaluated by an acute oral toxicity study using rats. The test material was given by gastric intubation. No deaths occurred in the separate tests of two lipstick formulations containing 0.005 percent Propyl Gallate up to an exposure of 5.0 g/kg of the formulation.[122,123] The third formulation, containing less than 1 percent Propyl Gallate, produced diarrhea in the test animals at all doses up to 10 ml/kg of the formulation. No deaths occurred at any dose. No lesions were found in the test animals at necropsy.[124]

Two suntan preparations, a sun protection stick and a suntan cream, each containing 0.003 percent Propyl Gallate, were evaluated by acute oral toxicity studies. Both were administered by gavage to 10 rats. The sun protection stick was administered as a 50 percent solution in olive oil at a single dose of 25 g/kg, and the suntan cream was administered full strength at a single dose of 50 ml/kg. Rats were observed for 14 days; no deaths or toxic effects resulted from the administration of either suntan preparation. The investigators concluded that the sun protection stick and suntan cream were practically nontoxic and nontoxic, respectively.[125,126]

Intraperitoneal Toxicity

The acute intraperitoneal (IP) toxicity of Propyl Gallate was studied in rats. Groups of 2 to 18 animals received single IP injections of 0.2 to 0.5 g/kg Propyl Gallate. The acute IP LD_{50} was determined to be 0.38 g/kg. Death usually occurred within 10 to 60 minutes postinjection and appeared due to asphyxia or cardiovascular failure. Necropsies of animals that died revealed dilatation of visceral and peripheral blood vessels, especially those leading to the adrenal glands, and inflated lungs.[118]

Primary Skin Irritation

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

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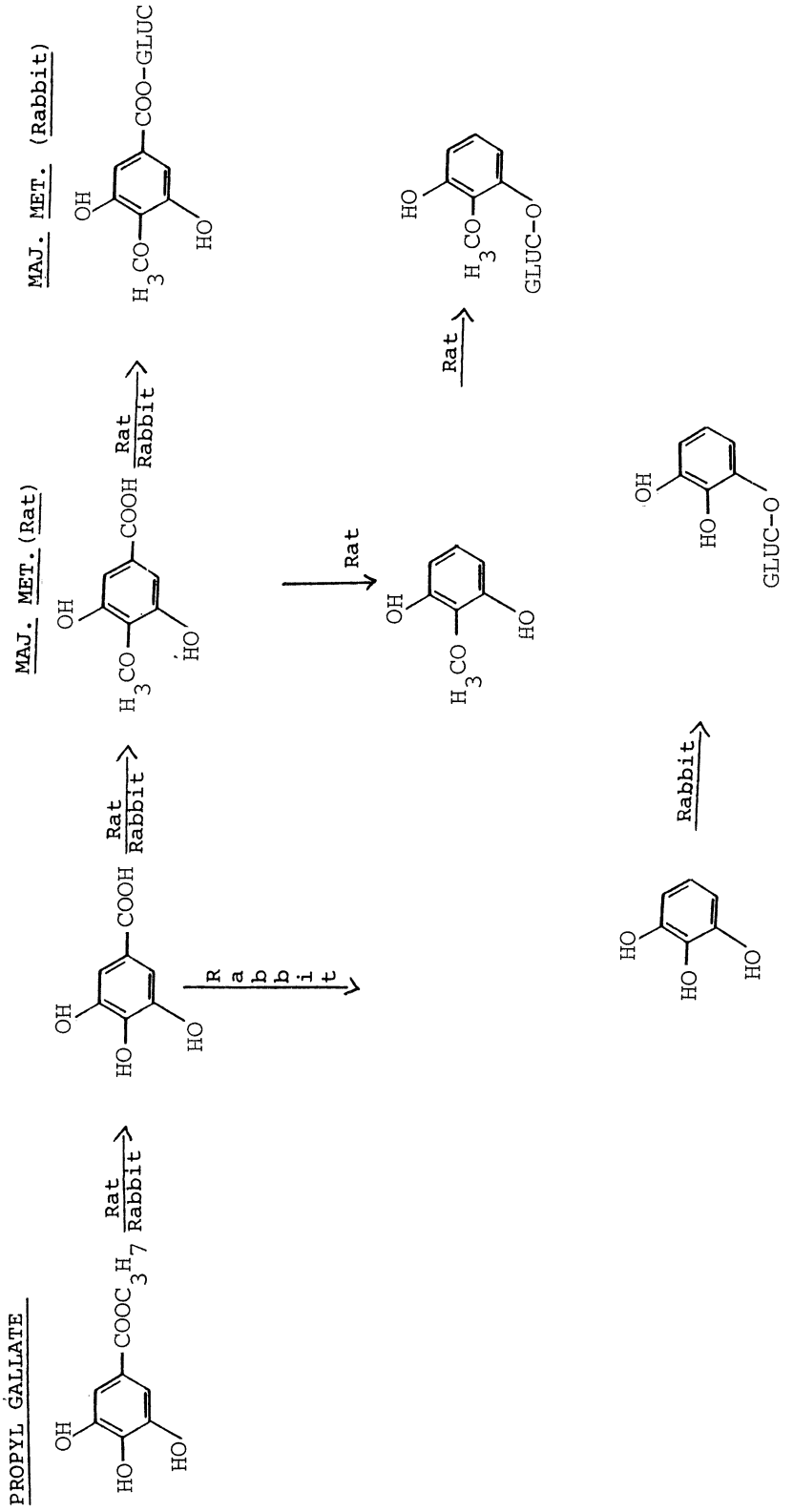


FIG. 2. Metabolic pathway of Propyl Gallate in rats and rabbits.

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TABLE 4. Acute Oral Toxicity of Propyl Gallate

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

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

In an early study, a 10 percent solution of Propyl Gallate in propylene glycol was applied to the shaved intact skin of guinea pigs for 48 hours. No local lesions or primary irritation were observed[10] (Table 5).

Propyl Gallate, at concentrations of 0.5 and 1.0 percent in saline, was injected intradermally into the shaved skin of each of 3 albino rabbits. Positive and negative controls were also included in the study. Ten minutes later, 10 mg/kg trypan blue were administered intravenously. Treated sites were observed 1.5 hours later for tissue irritation (based on the amount of tissue coloration). Propyl Gallate at 0.5 and 1.0 percent resulted in a mean irritation score of 2 (maximum score = 16), indicating that Propyl Gallate was practically nonirritating to local tissue[77] (Table 5).

A primary skin irritation test on the intact and abraded skin of 6 rabbits was conducted using a lipstick formulation containing less than 1 percent Propyl Gallate. The test material was applied for 24 hours under an occlusive wrap. Upon removal of the wrap, the test sites were scored for erythema and edema at 24 and 72 hours. No erythema was observed. A very slight edema at 3 intact and 3 abraded sites and a slight edema at 1 abraded site were observed at 24 hours, but none at 72 hours. The formulation gave a Primary Irritation Index (PII) of 0.33 and was considered not a primary irritant[132] (Table 5).

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

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TABLE 5. Primary Skin Irritation of Propyl Gallate

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

*PII, Primary Irritation Index.

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

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

Acute Eye Irritation

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

An acute eye irritation test on 6 rabbits was conducted using a lipstick formulation containing less than 1 percent Propyl Gallate. The left eye received 0.1 ml of the test formulation; the right eye was untreated and served as a control. A mild conjunctival erythema in 1 rabbit was reported. The latter was graded as a response of 2 (maximum score of 110). The lipstick formulation was not an eye irritant[135] (Table 6).

Two suntan preparations, a sun protection stick and a suntan cream, each containing 0.003 percent Propyl Gallate, were tested for acute eye irritation by the Draize technique.[136] A 0.1 g sample of each product (full strength) was instilled into the conjunctival sac of 9 rabbits. Three rabbits received no further treatment, the eyes of the second 3 were rinsed with water 2 seconds after instillation, and the eyes of the third 3 were rinsed 4 seconds after instillation. Reactions were scored at 24, 48, and 72 hours and 4 and 7 days. Six of the nine rabbits receiving the sun protection stick had conjunctival irritation (1+ on a scale of 0 to 3) at 24 hours. Only 2 rabbits had conjunctival irritation at 48 hours, and all eyes were clinically normal at 72 hours. Five of the nine rabbits receiving the suntan cream showed conjunctival irritation (1 on a scale of 0 to 3), and 2 had chemosis (1 on a scale of 0 to 4) at 24 hours. All eyes were normal at 48 hours. The products were not eye irritants[137,138] (Table 6).

TABLE 6. Acute Eye Irritation of Products Containing Propyl Gallate

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

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Six cosmetic formulations, each containing 0.003 percent Propyl Gallate, were tested for eye irritation as described in 16 CFR 1500.42. Six rabbits were used to evaluate each formulation; one eye of each rabbit received a 0.1 ml sample of the product and the other eye served as a control. One group of 6 rabbits also served as an untreated control. Reactions were scored on a standard Draize scale at 24, 48, and 72 hours and 7 days. The formulations produced no or very slight irritations, all of which progressively decreased to a 0 score at 72 hours. None of these formulations were eye irritants[139,140] (Table 6).

Subchronic Effects

Cutaneous Toxicity

Cutaneous toxicity was studied using Propyl Gallate, 20 percent in lanolin, applied daily, 5 times per week for 6 weeks to the ears of 53 male guinea pigs. Skin biopsies were performed weekly during treatment and at 4-day intervals for 2 weeks after discontinuation of treatment. Tissues were prepared for electron microscopic examination. Treatment with Propyl Gallate resulted in reversible hyperplasia of the epidermis.[141]

The effect of Propyl Gallate on skin depigmentation was studied in black guinea pigs. The test material was applied daily for 1 to 6 months at concentrations 0.1 to 10 percent to the epilated dorsal skin of groups of 2 to 5 animals. Positive (monomethyl ether of hydroquinone and tertiary butyl catechol) and negative (solvent) controls were also used. Depigmentation and irritation were assessed regularly; punch biopsies were also taken and examined microscopically. Propyl Gallate induced some irritation but did not result in depigmentation.[142]

Oral Toxicity

Rats and pigs (strain/breed and number not specified) were fed diets containing 0.035 to 0.5 percent and 0.2 percent Propyl Gallate, respectively, for 3 months. Animals were then killed and necropsied. Propyl Gallate, at the concentrations tested, had no effect on growth, reproduction, organ weights, blood chemistry values, morphology of blood cells, or histopathologic changes of tissues of treated animals when compared to controls.[119]

Propyl Gallate was included in the diets of mice and rats at doses of 170 and 340 mg/kg (mice) or 260 and 520 mg/kg (rats) for 2.5 months. Ingestion of Propyl Gallate resulted in decreased growth rates as well as reductions in serum catalase, peroxidase, and cholinesterase activities.[128]

Six groups of 12 weanling rats each were fed diets containing 0 to 0.5 percent Propyl Gallate for 6 weeks. Animals were then killed, blood samples were collected and analyzed, liver and adrenal glands were examined microscopically, and total lipid content of the liver was determined. Propyl Gallate had no significant effect on growth rate at any dose. Weights of the liver and adrenal gland were normal, and no pathologic changes could be attributed to treatment. Propyl Gallate had an insignificant effect on serum concentration of cholesterol and sodium, on the cholesterol content of the adrenal gland, and lipid content of the liver. Propyl Gallate did not produce significant toxic effects in rats when ingested and was considered safe for use in food.[143]

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Propyl Gallate, fed to rats for 1 or 3 months, did not affect development of enterokinase in the mucosa of the upper portion of the small intestine, nor did it affect pancreatic lipolytic enzyme secretion.[144]

Four groups of 8 rats each and one group of 7 rats received doses of 0 to 500 mg/kg per day Propyl Gallate by stomach tube for 1 week. Animals were killed 24 hours after the final dosing. Four additional groups of 6 rats each were maintained at the high dose (500 mg/kg per day) and killed 14 and 28 days after the last dosing. Histopathological examination and biochemical analyses were performed on the liver of all animals. Positive (carbon tetrachloride) and negative (arachis oil) controls were included in the study. Propyl Gallate had no effect on hepatic weight or on hepatic enzymic activity. Slight fatty change was observed in the liver of rats given 100, 200, and 500 mg/kg per day. This effect was not dose dependent and not statistically significant. At the highest dose, extensive fatty change was observed 24 hours after the final dosing, but the severity decreased significantly after 14 days of recovery. By 28 days, the liver of most animals had returned to normal. Propyl Gallate also significantly increased the number of abnormal mitotic figures in hepatocytes. At the highest dose tested, this effect persisted throughout the first 14 days of the recovery period but had disappeared by the twenty-eighth day posttreatment.[145]

Sensitization

Three separate tests were used to determine the sensitizing potential of Propyl Gallate in guinea pigs. In the first test, Propyl Gallate (5 percent in complete Freund's adjuvant) was administered intradermally every other day for 6 days into the clipped dorsal skin of 2 female guinea pigs. Ten days after the last injection, occlusive patches containing 0.1, 0.5, and 2 percent Propyl Gallate in alcohol were each applied to the clipped ventral skin for 24 hours. Sites were scored at 24 and 48 hours. No sensitization occurred at 0.1 percent, but it did occur at the other 2 test concentrations. Reactions gradually subsided within 7 to 10 days. Tests performed 3 months later using these sensitized guinea pigs gave similar responses. There was no cross-sensitivity with pyrogallol, gallic acid, or methyl gallate; there was weak cross-sensitivity with lauryl gallate.[146]

In the second study, 20 percent Propyl Gallate in alcohol was applied for 24 hours under occlusion to clipped shoulder skin of 2 guinea pigs every third day for 9 days. Two weeks after removal of the final induction patch, occlusive challenge patches containing 0.1, 1, or 5 percent Propyl Gallate were applied to the clipped ventral skin for 24 hours. Sites were scored at 24 and 48 hours. Mild to moderate irritation was produced by 1 and 5 percent Propyl Gallate at 24 hours and by 5 percent at 48 hours. When animals were retested 3 months later, severe reactions were observed.[146]

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

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Sites were scored at 24 and 48 hours. None of the Propyl Gallate-fed animals reacted to Propyl Gallate challenge patches, but all animals reacted to challenge with DNCB. Guinea pigs not orally dosed with Propyl Gallate developed mild or moderate to severe irritation to challenge patches containing 0.5 percent or 2 percent Propyl Gallate, respectively. At 0.1 percent, Propyl Gallate was nonsensitizing.[146]

Results of these three studies indicated that Propyl Gallate was a strong sensitizer when given intradermally. By the cutaneous route, it was less sensitizing and required a much longer induction time. Specific tolerance to Propyl Gallate-induced contact sensitization occurred following ingestion.[146]

Chronic Oral Toxicity

Ten groups of 10 to 20 weanling albino rats were fed diets containing either 0, 0.00117 to 2.34 percent Propyl Gallate, or an antioxidant mixture containing 2 percent Propyl Gallate for 2 years. Some animals were killed at various times throughout the study; these animals, along with animals that died, were necropsied. Growth, blood parameters, organ weights, and histopathological changes were monitored. Rats given 1.17 or 2.34 percent Propyl Gallate had significantly reduced growth rates, but growth of rats at lower concentrations was similar to controls. When the concentration of Propyl Gallate was lowered for these animals, growth returned to normal. No other gross effects were observed. Animals of the 1.17 and 2.34 percent Propyl Gallate groups had significantly lower hemoglobin values and erythrocyte counts. The only consistent abnormalities observed upon necropsy were mottled kidneys. On microscopic examination, tubular damage and the presence of albuminous casts were found in animals of the 1.17 and 2.34 percent groups. Rats fed these concentrations also had significantly higher mortality rates.[118]

Two groups of 20 guinea pigs each (14 males and 6 females) were fed diets containing 0 or 0.0117 percent Propyl Gallate for 14 to 15 months. Males and females were mated within each group after 1 year of feeding; 6 offspring were observed for 2 months following birth. Animals were observed and killed, and biological parameters were monitored. Propyl Gallate had no effect on growth rate, appearance, or reproduction. No abnormalities were found at necropsy or at histopathological examination of organs of Propyl Gallate-treated guinea pigs.[118]

Two groups of 5 and 7 dogs were fed diets containing 0 and 0.0117 percent Propyl Gallate, respectively, for 14 months. No alterations in behavior, appearance, and physical activity, as well as blood and urinary parameters, were found. The results indicated that, at the dose tested, Propyl Gallate did not change renal or hepatic function.[118]

The effect of Propyl Gallate on mortality was studied in rats. Six groups of 16 animals each were fed diets containing 0 to 5 percent Propyl Gallate for 2 years. Animals were killed at various times throughout the study and were necropsied along with deceased animals. None of the treated groups had significant differences in the number of animals alive after 2 years of feeding when compared to controls. The only significant pathological finding was patchy hyperplasia in the stomach of rats fed the 5 percent Propyl Gallate diet. Propyl Gallate was concluded to be safe for use in foods.[147]

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

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ous concentrations of anti-oxidants, resulting in effective concentrations of 0, 0.405, or 20.25 mg Propyl Gallate per kg diet. Rats were maintained on the diets for 1 year. Food consumption, body weight, mortality, appearance, and behavior were monitored. At 13 and 26 weeks, 3 rats of each sex from each group were killed and necropsied, and tissues were examined microscopically, as were all animals that died during the experiment. At the conclusion of the feeding study, the remaining animals were killed and necropsied. Propyl Gallate had no significant effects on growth rates or organ weights. A low incidence of renal tubular degeneration and glomerulonephritis was observed in Propyl Gallate-treated female rats.[39]

In a subsequent study, the investigators added the bread ingredients at the same doses directly to the basal diet of 14 groups of 15 rats each for 32 weeks instead of baking the bread ingredients prior to addition to the diet. No significant differences in body weight, hematological parameters, organ lesions, appearance, behavior, mortality, or tissue weight were found attributable to the ingestion of up to 20.25 mg Propyl Gallate per kg diet.[148]

Groups of rats and pigs (strain/breed unspecified) were given 0.035 to 0.5 percent and 0.2 percent Propyl Gallate, respectively, in the diet for more than 3 months until a few litters had been produced. All animals were then killed and necropsied. Propyl Gallate induced no significant changes in growth or reproduction. No significant abnormalities that could be attributed to ingestion of Propyl Gallate were observed at necropsy. In older rats at 0.035 percent Propyl Gallate and in a "few" controls, calcium deposits and tubular protein casts were found in the kidneys. These changes were not observed in rats fed higher concentrations of Propyl Gallate and were considered unrelated to the administration of Propyl Gallate. In rats and pigs on the 0.035 percent Propyl Gallate diet, organ weights and hematologic values did not differ significantly from controls.[119]

In a chronic feeding study, groups of 46 rats were fed diets containing either a mixture of food additives including Propyl Gallate or no additives. In the mixture, the dose of each compound was 35 times the average daily human consumption. There were no differences in weight gain, fertility, or survival between control and test animals.[149]

Three groups of 50 albino mice each were fed diets containing 0, 0.5, or 1.0 percent Propyl Gallate for 90 weeks. Body weights, feed consumption, and hematological parameters were monitored. All surviving mice were killed and necropsied at 21 months. No significant toxic effects were observed. No significant differences in body weight, growth, gross abnormalities, or hematological parameters were observed between test and control animals. The author noted that the 1 percent intake of Propyl Gallate corresponded to a dose of 1.5 g/kg per day, whereas the no-effect level reported by Orten et al.[118] corresponded to an intake of 0.05 g/kg per day.[150]

Phototoxicity

A phototoxicity test was used to evaluate a sun protection stick containing 0.003 percent Propyl Gallate. The product was applied full strength to one of the tape-stripped ears of each of 6 guinea pigs, the untreated ears serving as controls. One positive control with 8-methoxypsoralen and one unirradiated control with

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the sun protection stick were also maintained. Each guinea pig was exposed for 2 hours to UVA from two GE F8T5-BL lamps at a distance of 4 to 6 cm. Ears were evaluated for irritation 24 and 48 hours later. No irritation was seen in any of the 6 guinea pigs. The sun protection stick was not phototoxic under these test conditions.[151]

Mutagenesis

Three different assays, a host-mediated assay, a cytogenic assay, and a dominant lethal assay, were used to evaluate the mutagenicity of Propyl Gallate.

The host-mediated assay consisted of three parts: an acute in vivo test, a subchronic in vivo test, and an in vitro study. In the acute test, 0 to 200 mg/kg Propyl Gallate was administered orally to each of 10 mice. Positive and negative controls were used. Animals then received intraperitoneally 2 ml *S. typhimurium* strain TA 1530 and G 46, as well as 2 ml *S. cerevisiae* strain D 3 indicator organisms. Animals were killed 3 hours later; peritoneal fluid was removed, bacterial counts were made, and the number of mutants was recorded. In the subchronic test, each of 10 mice received orally 0 to 3500 mg/kg Propyl Gallate daily for 5 consecutive days. Within 30 minutes after the last treatment, animals were inoculated with indicator organisms and treated as above. In the in vitro study, 0 to 100 μg/ml Propyl Gallate was added to plates containing the indicator organisms. After incubation, the number of mutants was recorded. Propyl Gallate induced no significant increases in mutant or recombinant frequencies with *S. typhimurium* or *S. cerevisiae* in these in vitro or in vivo host-mediated assays.[131]

The cytogenic assay also consisted of acute and subchronic in vivo tests and an in vitro study. In the acute test, groups of 15 rats were given 5 to 5000 mg/kg Propyl Gallate by gastric intubation. Four hours later, each animal received intraperitoneally 4 mg/kg colchicine in order to arrest bone marrow cells in C-mitosis. Five animals at each dose were killed at 6, 24, and 48 hours. Bone marrow was removed, and the chromosome preparations were scored for abnormalities. Positive and negative controls were used. In the subchronic study, groups of 5 mice received 0 to 5000 mg/kg Propyl Gallate daily for 5 consecutive days. Animals were killed 6 hours following the last dosing and treated as above. In the in vitro study, 0.5 to 50 μg/ml Propyl Gallate were added to human embryonic lung cultures in anaphase. Positive and negative controls were used. Chromosomal damage was then scored. Propyl Gallate induced no detectable significant aberrations in the bone marrow metaphase chromosomes of rats and induced no significant aberrations in the anaphase chromosomes of human tissue culture cells in vitro.[131]

In the dominant lethal assay, groups of 10 male rats received orally 0 to 5000 mg/kg Propyl Gallate once (acute study) or daily for 5 consecutive days (subchronic study). Positive and negative controls were used. Following treatment, males were mated with 2 virgin females per week for 7 or 8 weeks. Pregnant dams were killed 14 days after separation from treated males; the uteri were examined for resorption sites, late fetal deaths, and total implantations. No dose–response or time-trend patterns that would suggest a dominant lethal effect for Propyl Gallate were observed; Propyl Gallate was nonmutagenic under the study conditions.[131]

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

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

The cytogenetic activity of Propyl Gallate was tested in a diploid human embryo fibroblast cell line. Propyl Gallate was added to cell cultures at doses of 0 to 0.0212 mg/ml for 26 to 48 hours. Chromosome preparations were then made, and aberrations as well as sister chromatid exchanges were scored. At the highest dose tested, Propyl Gallate was toxic to cells. At the lower dose (0.0021 mg/ml), Propyl Gallate did not induce significant chromosomal aberrations or sister chromatid exchanges.[153]

In an Ames test, Propyl Gallate was tested for mutagenic activity in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, as well as *E. coli* strain WP2 at concentrations of 0.03 to 1000 μg/plate. Assays were performed in the presence and absence of Aroclor 1254-induced rat hepatic microsomes. Propyl Gallate was toxic to all strains at 333 and 1000 μg/plate. No significant mutagenicity was produced either with or without metabolic activation in all indicator organisms.[154]

In another Ames test, Propyl Gallate was added to cultures of *S. typhimurium* strains TA98 and TA100 at concentrations of 0.1 to 10 mM. Assays were performed in the presence and absence of Aroclor 1254-induced rat hepatic microsomes. Propyl Gallate was nontoxic to cells except at the highest test concentration and did not induce significant mutagenic frequencies both with and without activation when compared to solvent control values.[103]

Shelef and Chin[104] also used the Ames test to study the mutagenicity of Propyl Gallate. The test material was added to cultures of *S. typhimurium* TA98 and TA100 at doses of 0 to 50 μg/plate. Assays were performed in the presence and absence of Aroclor 1254-induced rat liver microsomes. Whereas Propyl Gallate was toxic to cells at the highest dose tested, no mutagenicity was found both with and without metabolic activation.

In a Japanese study, the Ames test (with TA100 and TA98), a *rec*-assay (with *Bacillus subtilis*), a chromosomal aberration/sister chromatid exchange assay (in hamster lung and human embryo fibroblasts), an in vivo chromosomal aberration test (in rat bone marrow), and a silkworm mutation assay were used to determine the mutagenicity of Propyl Gallate. In all assays, Propyl Gallate was assayed without metabolic activation. Propyl Gallate was mutagenic in the *rec*-assay and in the hamster lung chromosomal aberration assay. In all other test systems, Propyl Gallate was nonmutagenic.[155]

Mutagenesis Enhancement

Rosin and Stich[103] reported that Propyl Gallate enhanced the mutagenic effect of N-hydroxy-2-acetylaminofluorine and 4-nitroquinoline-1-oxide (4-NQO) in *S. typhimurium* strains TA98 and TA100, respectively. Bacterial cultures were suspended in a mixture of Propyl Gallate, chemical to be tested, dimethyl sulfoxide, and saline. A 580 to 700 percent increase in mutation frequency was observed without metabolic activation only. Propyl Gallate also induced a 700 percent increase in the mutagenic frequency of 4-NQO in TA98 and was also toxic to cells (only 16 percent cell survival). Therefore, Propyl Gallate may enhance the reduction of 4-NQO to a mutagenic product.

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Carcinogenesis and Tumorigenesis

Propyl Gallate was tested for its ability to induce pulmonary tumors in groups of 30 strain A mice. The test material was injected intraperitoneally at doses of 0.6 or 2.4 g/kg, 3 times weekly for 8 weeks (24 injections). Positive, negative, and vehicle controls were also included in the study. At 24 weeks, animals were killed, and the lungs were examined for tumor formation and other abnormalities. No significant differences were observed in the number of pulmonary tumors between test and control animals.[156]

Propyl Gallate was tested for carcinogenicity by the National Toxicology Program (NTP) by feeding diets containing 6,000 or 12,000 ppm Propyl Gallate to 50 F344 rats and 50 B6C3F1 mice of each sex for 103 weeks. Control groups of 50 rats and mice of each sex were kept. Tumors of the preputial gland, pancreatic islet cells, and adrenal gland (pheochromocytomas) were found in low-dose male rats at significantly higher levels than in controls. However, they were not increased in the high-dose males and were within the range of historical controls. Similarly, thyroid follicular cell tumors occurred in the dosed male rats but were not significant in comparison to untreated controls and comparable to historical controls. Rare brain tumors were found in two low-dose female rats; none were found in the high-dose group. Adenomas of the mammary gland also occurred in the high-dose female rats but were not significant compared to controls. Adenomas of the liver occurred in the high-dose female mice at a significantly higher level than in the concurrent controls, but this incidence was within the historical range for this tumor. All of these tumors were considered unrelated to the administration of Propyl Gallate. The high-dose male mice had a significant increase in malignant lymphomas relative to concurrent controls but not statistically significant when compared with the historical rate. Propyl Gallate was not considered to be carcinogenic in either species, although the increased number of malignant lymphomas in male mice may have been related to the administration of Propyl Gallate.[157]

Teratogenesis

The teratogenic effect of Propyl Gallate was studied in 9 female rats by Telford et al.[158] Animals were mated and then given a total dosage of 0.5 g per rat in the diet. On the twenty-second day of gestation, the rats were killed, and the young were removed for study. At the dose tested, Propyl Gallate was nontoxic to the pregnant rats, although it substantially increased fetal resorption rates (18.3 percent resorption; 77.7 percent litters with resorptions) when compared to controls (10.6 percent resorption; 40.8 percent litters with resorptions).

The teratogenic effects of Propyl Gallate were studied in rats, mice, and hamsters. Twelve groups of 22 to 25 pregnant animals were given orally 3.0 to 300 mg/kg (rats, mice) or 2.5 to 250 mg/kg (hamsters) Propyl Gallate. Doses were given daily from Day 6 to Day 10 (hamsters) or Day 15 of gestation (rats, mice). Positive (aspirin) and negative (corn oil) controls were used. Animals were observed for signs of toxicity, and body weight was monitored. On gestation Day 14 (hamsters), 17 (mice), or 20 (rats), all dams were killed and the fetuses removed. Numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. Urogenital tracts of females were examined for abnormalities. All fetuses were examined for visceral, skeletal, and external abnormalities. Oral administration of up to 250 mg/kg Propyl Gallate for 5 consecutive days in hamsters

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or up to 300 mg/kg Propyl Gallate for 10 consecutive days in rats and mice had no effect on nidation or on maternal or fetal survival. The number of visceral, skeletal, and external abnormalities observed in the test group fetuses did not differ significantly from that of negative control groups.[159]

A similar teratological study was performed on 4 groups of 20 to 50 pregnant rabbits given orally 2.5 to 250 mg/kg Propyl Gallate daily from Day 6 to Day 18 of gestation. Positive (6-aminonicotinamide) and negative (corn oil) controls were used. Ingestation of up to 250 mg/kg Propyl Gallate for 13 consecutive days during gestation had no effect on nidation or maternal or fetal survival. The number of visceral, skeletal, and external abnormalities observed in the test group fetuses did not differ significantly from negative control groups.[160]

Desesso[115] studied the teratological effects of Propyl Gallate on rabbits. Each rabbit received a subcutaneous injection of 634 mg/kg Propyl Gallate in a water–ethanol vehicle on the twelfth gestational day. Two control groups were kept, one receiving the vehicle and the other remaining untreated. On the twenty-ninth day, the rabbits were killed and examined for resorptions and fetuses. No malformations and a low incidence of resorption were found in the 6 litters obtained from Propyl Gallate-treated rabbits. Weights of the fetuses in the Propyl Gallate group were significantly higher than those of the negative controls; however, they were similar to those of the vehicle controls.

In another teratogenesis study, groups of 18 to 20 pregnant Wistar rats were fed diets containing 0, 0.4 percent (0.35 g/kg), 1 percent (0.88 g/kg), or 2.5 percent (2.04 g/kg) Propyl Gallate starting on Day 1 of gestation. On the twentieth day of gestation, 13 of 18 rats of the 2.5 percent group and 15 of 20 rats of the other groups were killed for fetal examination. Implantation sites and numbers of live and dead fetuses were counted; examinations of fetuses for organ and skeletal anomalies were then performed. The remaining dams from each group were allowed to give birth. Offspring were observed for 8 weeks, then killed, and tissues were examined microscopically for visceral and skeletal abnormalities. At the highest concentration tested, maternal body weight and feed consumption were significantly lower than those of controls. However, no other signs of toxicity were observed in these rats. Body weight of fetuses at the highest concentration of Propyl Gallate was reduced but not significantly so. There was no difference in fetal mortality between control and test rats. Additionally, no significant incidence of external or internal organ abnormalities occurred in test fetuses. Although skeletal abnormalities were observed in some of the fetuses of Propyl Gallate-treated rats, they were considered to be spontaneous. The only possible compound-related finding was a significant number of fetuses obtained from the 2.5 percent group with an insufficient number of caudal vertebrae. The only significant postnatal effect produced by Propyl Gallate was decreased viability in the 1 and 2.5 percent dose groups; this was due to cannabilism of the newborn by the dams. No behavioral or morphological changes were observed in the newborns from test mothers. Propyl Gallate was nonteratogenic.[130]

CLINICAL ASSESSMENT OF SAFETY

Irritation and Sensitization

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

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

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

Propyl Gallate, 20 percent in alcohol, was applied to the forearms of 10 white subjects daily for about 24 days. Sites were examined twice weekly. For the first 14 days, there were no signs or complaints of irritation. During the last 10 days, 5 of the 10 subjects complained of pruritis and erythema. Three of these reactions were mild and subsided within a few days. The other 2 subjects developed a skin eruption that progressed up the arm and onto the trunk; the reaction required 3 weeks to heal. The investigators then applied single 48-hour patches containing 2 percent Propyl Gallate to 2 of the mildly sensitized reactors and to 25 nonsensitive control subjects. Both sensitized subjects reacted mildly to the patch, whereas none of the control subjects reacted to Propyl Gallate. Propyl Gallate was a contact sensitizer at high concentrations (10 percent). However, human tolerance to low Propyl Gallate concentrations may be the result of repeated oral exposures to low doses of Propyl Gallate in food[146] (Table 7).

A repeat insult patch test (RIPT) on a total of 16 subjects was conducted using a lipstick formulation containing less than 1 percent Propyl Gallate. The test material "sufficient to cover a Webril pad" was applied at 48- and/or 72-hour intervals to the upper arms and covered for the first 24 hours between applications. Each site was scored at 48 and/or 72 hours when new patches were applied. The 22-day induction period was followed by a 12-day rest period before application of a 24-hour occlusive challenge patch. No irritation was observed in the 15 subjects who completed the test program, but 1 subject had a mild sensitization reaction following the challenge application at an adjacent site. The test report stated that the score did not suggest "significant dermatotoxicity"[162] (Table 7).

Two lipstick formulations, each containing 0.005 percent Propyl Gallate, were tested for cumulative irritancy using 14 subjects, of which 12 completed the test. Approximately 0.2 g of each lipstick and 0.3 ml of 2 reference materials (of low and high irritancy) were applied daily by occlusive patch to the back of each panelist. Patches were removed after 23 hours and scored 1 hour later, and the procedure was repeated for 21 consecutive days. The total calculated scores of the 2 formulations (based on 10 subjects) were 1.67 and 29.51, respectively, placing them in the "essentially nonirritating" classification (score of 0 to 49 on a maximum scale of 630). The total calculated scores for the low and high irritancy reference materials were 2.50 and 616.67, respectively[161] (Table 7).

Three suntan preparations, an oil, a cream, and a sun protection stick, were evaluated for irritation and sensitization by a modified Draize-Shelanski repeat insult patch test.[163-165] Each preparation contained 0.003 percent Propyl Gallate. Topical, occlusive patches were applied to the upper backs of the panelists on Monday, Wednesday, and Friday for 3 consecutive weeks. Sites were scored (scale of 0 to 4) prior to each patch application. This induction phase was followed by a 2-week nontreatment period. Two consecutive 48-hour challenge patches were then applied to adjacent sites and scored at 48 and 96 hours. The suntan oil, tested on 151 subjects, produced 8 scores of 1 and 2 scores of 2 on induction and no positive reactions on challenge. The suntan cream and sun pro-

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TABLE 7. Clinical Irritation and Sensitization of Propyl Gallate

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

*RIPT, Repeat Insult Patch Test.

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

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

Photosensitivity/Phototoxicity

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

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

The photocontact sensitization of a sun protection stick containing 0.003 percent Propyl Gallate was evaluated using 25 subjects. A 0.2 ml sample of the sun stick was applied to the stripped skin of the back (one 2-inch square) of each subject. Sites were then exposed to three MEDs of xenon solar-simulating radiation and subsequently occluded. This procedure was repeated every 48 hours for 5 applications. After a 10-day rest, subjects were challenged on both normal and stripped skin in the same manner; however, this time the radiation was filtered through window glass. Sites were again occluded and evaluated at 24, 48, and 72 hours. No reactions were observed. The sun protection stick was not a photosensitizer under the test conditions[174] (Table 8)

Seven cosmetic formulations, including five sunscreens, were tested for photosensitization in 26 to 28 subjects (Table 8). Each formulation contained 0.003 percent Propyl Gallate. Occlusive patches containing 0.2 g of each product were applied to the volar arms of the subjects for 24 hours. Patches were then removed and sites were scored for irritation (scale of 0 to 4). One forearm of each subject was irradiated with four GE F40 BL lamps for 15 minutes, resulting in a

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TABLE 8. Clinical Photosensitivity/Phototoxicity of Propyl Gallate

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

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total UVA dosage of 4,400 $\mu W/cm^2$; the other forearm served as the nonradiated control. This procedure was repeated 3 times per week for 10 applications/radiations. After an 11- to 20-day rest, adjacent sites were challenged with a 24-hour patch application followed by radiation. These sites were scored 24 and 48 hours later. Six of the formulations produced only slight transient erythemal reactions (scores of ±, 1); the seventh also produced slight reactions except for a score of 2 (erythema and edema) on the second induction patch. No subsequent reactions were observed. These formulations did not produce photosensitization in humans[166-172] (Table 8).

Each of these 7 formulations was also tested for phototoxicity in 10 subjects (Table 8). Occlusive patches containing 0.2 g samples of each product were applied to the scrubbed, tape-stripped volar arms for 24 hours. Sites were scored on patch removal, and one arm of each subject was then irradiated with UVA light for 15 minutes for a total dose of 4,400 $\mu W/cm^2$. Sites were scored again immediately following, 24 and 72 hours, and 7 days after radiation. Four of the formulations produced no reactions; the other three produced only slight transient reactions. No phototoxicity was produced by these formulations.[166-172]

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

A suntan oil containing 0.003 percent Propyl Gallate was evaluated by a 2-day controlled use test. Each of the 78 subjects applied the oil to exposed parts of the body at 30 minute intervals for 2 hours of continuous sun exposure (11:30 am to 1:30 pm). Subjects were required to enter the pool for 10 minutes at the end of each hour. These procedures were repeated the second day. Any reactions immediately, 24, or 48 hours after application were noted. No clinically significant reactions were observed; the product was considered safe for intended use[176] (Table 8).

Oral Toxicity

A man ingested 0.5 g Propyl Gallate daily for 6 consecutive days. Urine was collected during this time and for 6 days after the final administration. The urine was negative for albumin, abnormal sedimental contents, red blood cells, and casts. The authors concluded that Propyl Gallate was safe and effective as an antioxidant in medicinal and pharmaceutical preparations.[10]

Nine infants in a pediatric ward of a hospital were found to have significant methemoglobinemia. A fat preservative in an infant formula was considered the probable source of toxicity. When the preservative was removed from these infants' diet, methemoglobin concentrations returned to normal within 48 to 96 hours. The preservative was identified as a mixture of BHA, BHT, and Propyl Gallate. In addition, age was an important factor in respect to the toxicity of phenolic compounds, since only newborn babies (6 to 15 weeks old) and not older babies

were affected by the preservative in the formula. Pyrogallol, which is chemically related to Propyl Gallate, had been previously implicated in methemoglobinemia.[177]

SUMMARY

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

In cosmetics, Propyl Gallate is employed as an antioxidant to stabilize vitamins, essential oils, perfumes, fats and oils. Although it may be used alone, it is generally used in combination with other antioxidants. According to the industry's voluntary submissions to the FDA in 1981, Propyl Gallate alone is used in over 118 cosmetic products at concentrations up to 5 percent. Most of these formulations, however, contain less than 0.1 percent Propyl Gallate. Available test information indicates that much lower concentrations are actually used.

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

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

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

Acute animal toxicity studies indicate that Propyl Gallate is slightly toxic when ingested and practically nontoxic when applied to the skin. Findings in subchronic studies include: 20 percent Propyl Gallate induces reversible epidermal changes when applied to the skin of guinea pigs for 6 weeks; this ingredient does not induce depigmentation when applied to the skin of black guinea pigs for 1 to 6 months; and Propyl Gallate is practically nontoxic or slightly toxic when ingested at concentrations up to 0.5 percent or doses up to 500 mg/kg. Propyl Gallate is a strong sensitizer when tested intradermally, less sensitizing when

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

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

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

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

Propyl Gallate was nontumorigenic when injected intraperitoneally in strain A mice at doses up to 2.4 g/kg 3 times weekly for 8 weeks. In a recently completed bioassay, the National Toxicology Program reported that Propyl Gallate was noncarcinogenic in mice and rats, although an increased incidence of malignant lymphomas in male mice may have been related to the administration of Propyl Gallate.

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

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

DISCUSSION

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

CONCLUSION

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

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

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

INTRODUCTION

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

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

CHEMISTRY

Definition and Structure

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

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

Chemical and Physical Properties

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

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

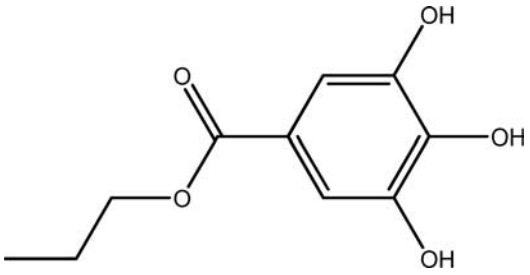


FIGURE 1
Chemical structure of Propyl Gallate (Gottshcalck and McEwen 2004).

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

TABLE 1
Physical and chemical properties of Propyl Gallate

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

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

Method of Manufacture

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

Analytical Methods

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

Reactivity

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

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

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

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

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

The oxidation of Propyl Gallate during free-radical

TABLE 2
Analytical methods used in Propyl Gallate determination

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

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

USE

Cosmetic Use

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

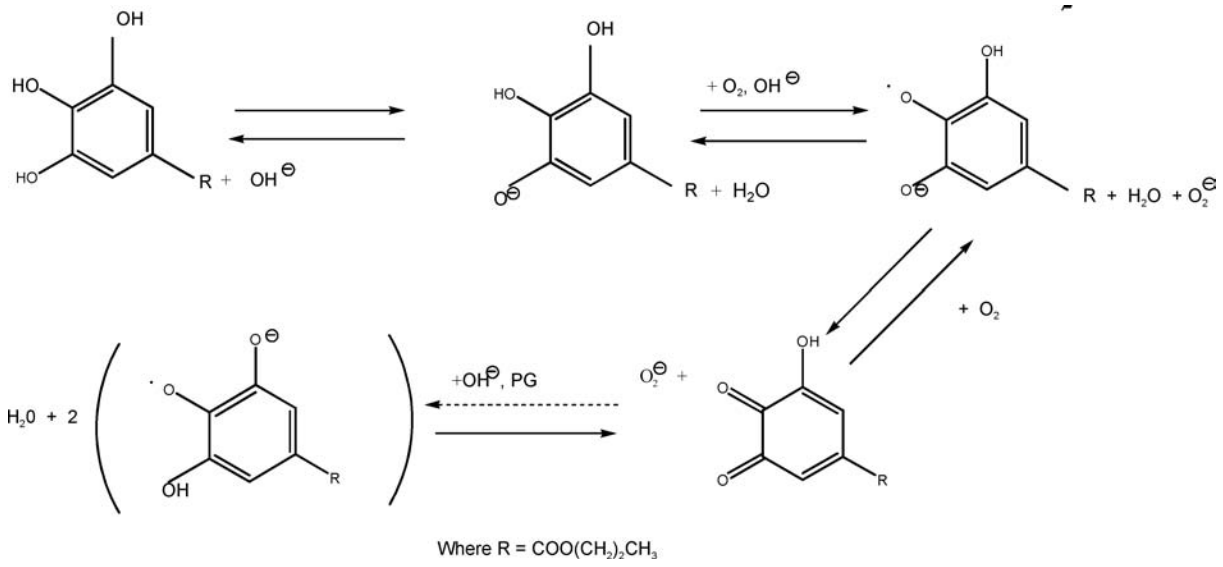


FIGURE 2
Oxidation of Propyl Gallate during free-radical scavenging suggested by Forgo and Buchi (1970).

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

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

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

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

NONCOSMETIC USE

Food

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

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

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

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

BIOLOGICAL ACTIVITY

Absorption, Metabolism, and Excretion

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

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

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

Antioxidant-Related Effects

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

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

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

(*Continued on next page*)

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

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

*No longer a category.

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

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

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

Antibacterial Activity

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

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

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

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

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

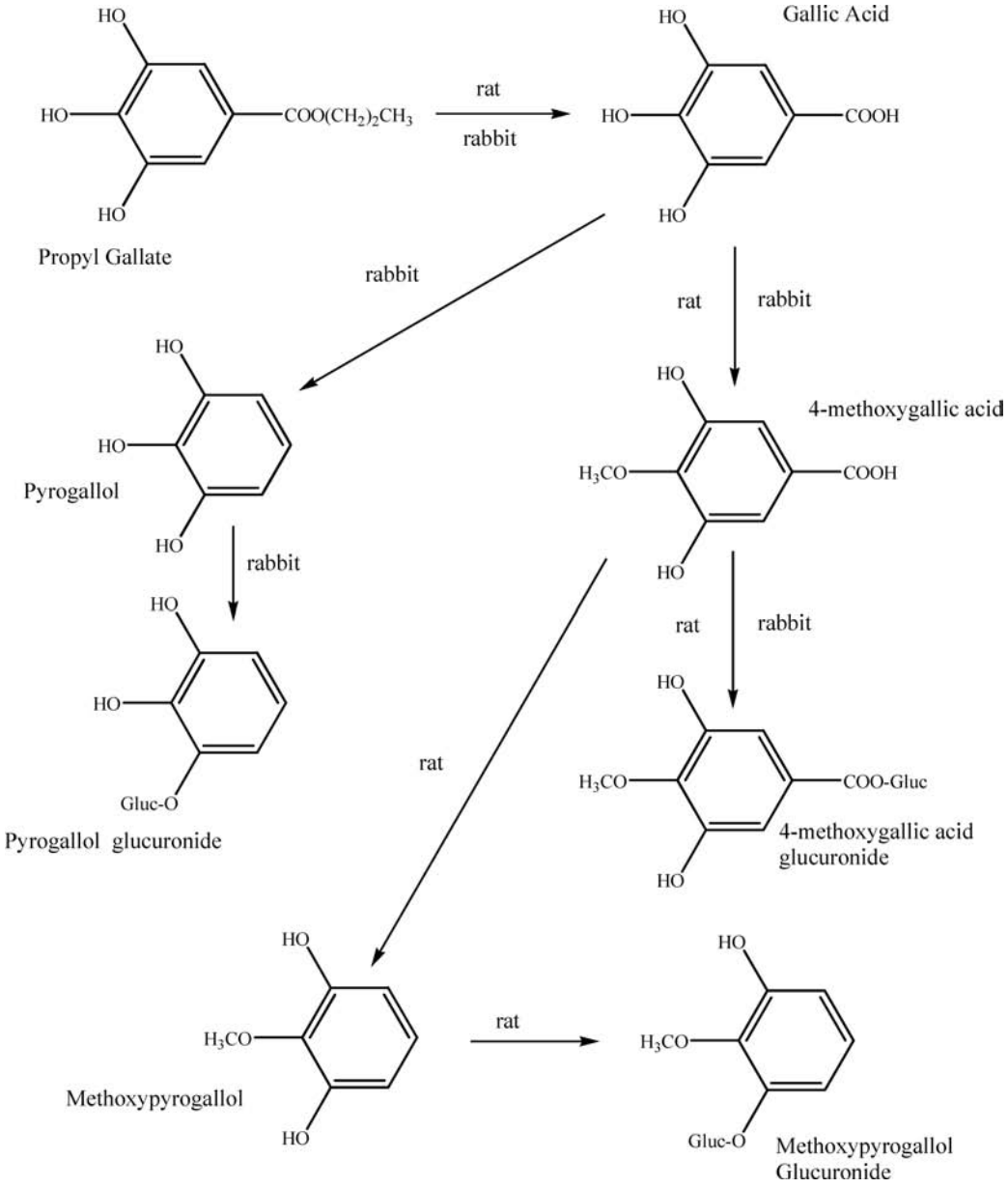


FIGURE 3
Metabolism of Propyl Gallate in rats and rabbits (after Dacre 1960).

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

Antifungal Activity

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

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

Effects on Enzymes

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

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

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

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

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

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

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

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

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

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

Effects on Prostaglandins/Anti-inflammatory Effects

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

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

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

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

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

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

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

Cellular/Tissue Effects

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

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

Hepatotoxicity/Hepatoprotection

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

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

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

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

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

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

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

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

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

Coagulant Effects

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

Neurological/Neuromuscular Effects

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

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

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

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

Anticariogenesis

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

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

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

Ionizing/Ultraviolet Radiation Protection

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

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

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

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

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

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

Chemoprotection

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

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

ANIMAL TOXICOLOGY

Acute Effects

Oral Toxicity

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

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

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

TABLE 4
Acute oral toxicity of Propyl Gallate

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

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

Intraperitoneal Toxicity

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

Dermal Irritation

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

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

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

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

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

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

TABLE 5
Acute dermal irritation of Propyl Gallate

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

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

Acute Ocular Irritation

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

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

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

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

TABLE 6
Acute ocular irritation—product tests

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

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

Subchronic Effects

Oral Toxicity

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

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

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

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

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

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

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

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

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

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

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

Dermal Toxicity

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

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

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

Chronic Oral Toxicity

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

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

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

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

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

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

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

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

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

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

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

Dermal Sensitization

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

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

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

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

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

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

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

Phototoxicity

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

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

GENOTOXICITY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Mutagenesis Enhancement

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

Antimutagenesis

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

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

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

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

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

CARCINOGENICITY

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

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

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

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

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

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

Anticarcinogenesis/Antitumorigenesis

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

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

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

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

Radiation Coeffects

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

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

Inhibition of Nitrosamine Formation

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

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

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

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

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

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

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

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

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

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

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

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

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

Inhibition of Developmental and Reproductive Toxicity

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

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

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

CLINICAL ASSESSMENT OF SAFETY

Irritation and Sensitization

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

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

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

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

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

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

Photosensitivity/Phototoxicity

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

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

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

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

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

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

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

[a]RIPT, repeat-insult patch test.

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

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

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

TABLE 8
Clinical photosensitivity/phototoxicity of Propyl Gallate

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

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

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

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

Case Reports

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY

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

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

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

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

CONCLUSION

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

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