Amended Safety Assessment of Pyrogallol 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 Christina Burnett, M.S., Senior Scientific Analyst/Writer, CIR.

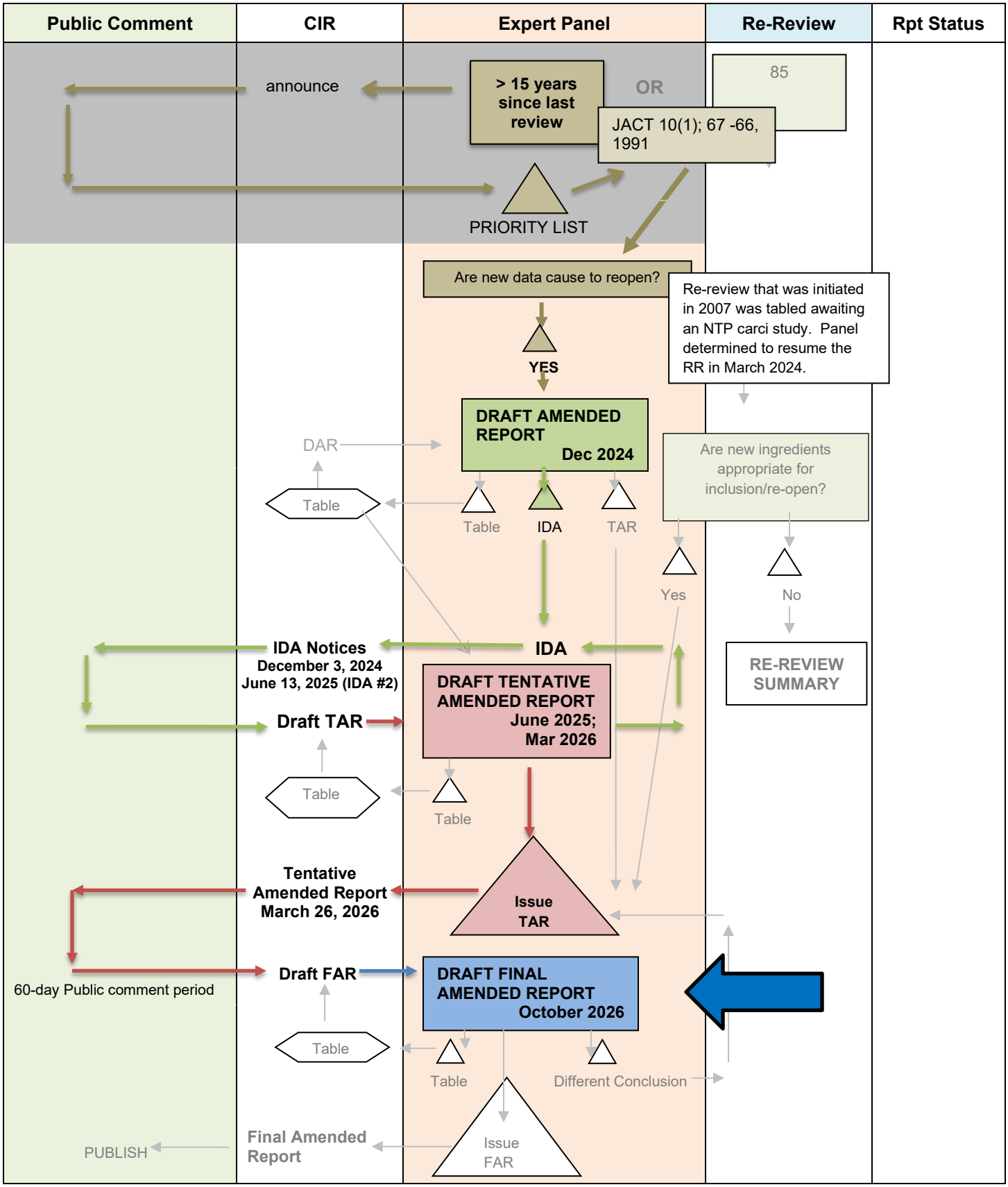
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RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Pyrogallol

MEETING October 2026



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, M.S., Senior Scientific Analyst/Writer, CIR
Date: September 11, 2026
Subject: Amended Safety Assessment of Pyrogallol as Used in Cosmetics

Enclosed is the Draft Final Amended Report on the Safety Assessment of Pyrogallol as Used in Cosmetics. (It is identified as *report_Pyrogallol_102026* in the pdf document). At the March 2026 meeting, the Panel issued a Tentative Amended Report for this hair dye ingredient with the conclusion that the available data are insufficient to make a determination of safety under the intended conditions of use as a cosmetic ingredient. The additional data needs are:

- Maximum concentration of use in hair dye formulations
- Genotoxicity studies, with metabolic activation, that test for the formation of DNA adducts

Since the March meeting, CIR has received no unpublished data. Comments received from the Council on the Tentative Amended Report have been addressed (*PCPCcomments_Pyrogallol_102026* and *response-PCPCcomments_Pyrogallol_102026*). An updated literature search identified additional relevant references, which have been incorporated into the report. The new data have been highlighted to assist in your review.

Additional supporting documents for this report package include the original report (*originalreport_Pyrogallol_102026*), the 2007 re-review document (*originalRR2007_Pyrogallol_102026*), a flow chart (*flow_Pyrogallol_102026*), report history (*history_Pyrogallol_102026*), a search strategy (*search_Pyrogallol_102026*), a data profile (*dataprofile_Pyrogallol_102026*), transcripts from the recent meetings (*transcripts_Pyrogallol_102026*), and the minutes from all the meetings at which Pyrogallol were discussed during the original reviews (*originalminutes_Pyrogallol_102026*).

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

Pyrogallol History

1991– The CIR Final Report on the Safety Assessment of Pyrogallol was published in the *Journal of the American College of Toxicology*. The Panel concluded that Pyrogallol is safe as a cosmetic ingredient in the present practices of use and concentration

June 2007 – A re-review of the available literature was performed. The Panel tabled the re-review to await the completion of carcinogenicity studies performed by the National Toxicology Program (NTP).

March 2024 – Review of the available published literature since 2007 was conducted in accordance to CIR Procedures regarding re-review of ingredients after ~15 years. The Panel reopened the safety assessment to include the data from the NTP studies and to add other new relevant data to report

December 2024 – The Panel issued an IDA for Pyrogallol. The following information is required to determine the safety of this hair dye:

- Maximum concentration of use
- Dermal irritation and sensitization data at maximum concentration of use for non-hair dye uses
- Ocular irritation data at maximum concentration of use for products used around the eyes

June 2025 - The Panel issued a second IDA for Pyrogallol. The additional data needed to determine safety for this ingredient are:

- Maximum concentration of use
- Genotoxicity studies, with metabolic activation, that test for damage to DNA adducts
- Dermal irritation and sensitization data at maximum concentration of use for non-hair dye uses
- Clarification on the type of use around the eyes
- Ocular irritation data at maximum concentration of use for products used around the eyes

March 2026 - The Panel issued a Tentative Amended Report for public comment with the conclusion that the available data are insufficient to make a determination of safety for Pyrogallol. The additional data needed to determine the safety of this ingredient are:

- Maximum concentration of use in hair dye formulations
- Genotoxicity studies, with metabolic activation, that test for the formation of DNA adducts

Pyrogallol Data Profile* – October 2026 – Christina Burnett																														
				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
Pyrogallol	XO	O	XO	X	X	O	XO	O		XO			O	O	XO	XO	XO		X	XO			XO	O			O	XO	

* "X" indicates that new data were available in a category for the ingredient. "O" indicates data were reported in the original safety assessment.

Pyrogallol

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Pyrogallol	87-66-1	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Search Strategy

PubMed

(pyrogallol) OR (1,2,3-trihydroxybenzene) OR (1,2,3-benzenetriol) OR (87-66-1[EC/RN Number]) – 1493 hits; searches further limited with the terms “carcinogenicity”, “genotoxicity”, “toxicity”, “dermal” – relevant studies are summarized above.

ECHA

Entry for CAS # 87-66-1 resulted in finding a dossier for Pyrogallol. Pertinent data not found in the original report is summarized in the report.

LINKS

Search Engines

- Pubmed - http://www.ncbi.nlm.nih.gov/pubmed
  - appropriate qualifiers are used as necessary
  - search results are reviewed to identify relevant documents
- Connected Papers - https://www.connectedpapers.com/
- DeepDyve - https://www.deepdyve.com/

Pertinent Websites

- wINCI - https://incipedia.personalcarecouncil.org/winci/ingredient-custom-search/
- FDA Cosmetics page - https://www.fda.gov/cosmetics
- eCFR (Code of Federal Regulations) - https://www.ecfr.gov/
- FDA search databases: https://www.fda.gov/industry/fda-basics-industry/search-databases
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras
- SCOGS database: https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database
- Inventory of Food Contact Substances Listed in 21 CFR: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=IndirectAdditives
- Drug Approvals and Database: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases
- FDA Orange Book: https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book
- OTC Monographs - https://dps.fda.gov/omuf
- Inactive Ingredients Approved For Drugs: https://www.accessdata.fda.gov/scripts/cder/iig/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- EUR-Lex - https://eur-lex.europa.eu/homepage.html
- Scientific Committees (SCCS, etc) opinions: https://health.ec.europa.eu/scientific-committees_en https://health.ec.europa.eu/scientific-committees/scientific-committee-consumer-safety-sccs_en
- ECHA (European Chemicals Agency – REACH dossiers) – https://echa.europa.eu/
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- EFSA (European Food Safety Authority) - https://www.efsa.europa.eu/en
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) IRIS library - https://apps.who.int/iris/
- a general Google and Google Scholar search should be performed for additional background information, to identify references that are available, and for other general information - www.google.com https://scholar.google.com/

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 7, 2026

SUBJECT: Tentative Report: Safety Assessment of Pyrogallol as Used in Cosmetics (release date: March 26, 2026)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of Pyrogallol as Used in Cosmetics.

Cosmetic Use; Summary – The European regulations are for "cosmetic products" not "cosmetic ingredients" as stated in the Cosmetic Use section and Summary.

Genotoxicity – Please correct: "results Ames tests were negative" (add the word "in")

Anti-Cancer Activity – Please indicate the concentrations at which the effects were observed. Currently, it just states the ranges of concentrations studied (0-90 µM). At what concentration were the effects statistically significantly different from the controls?

Summary – As only one ingredient is included in this report, please correct "reviewed these ingredients" to "reviewed this ingredient".

Please correct: "hyperplasia for the forestomach" ("for" should be "of")

Table 3 – In Table 3, where more details about a study should be included, please state all the concentrations that were tested. This would be especially helpful for reference 22 in which the results state that "Pyrogallol induced significant levels of chromosomal aberrations at <80 µM". What were the concentrations tested that were less than 80 µM (a similar order of magnitude, or much lower)?

Pyrogallol – October 2026 – Christina Burnett	
Comment Submitter: Jaap Venema, Personal Care Products Council **Date of Submission: April 7, 2026**	
Comment	**Response/Action**
Cosmetic Use; Summary - The European regulations are for "cosmetic products" not "cosmetic ingredients" as stated in the Cosmetic Use section and Summary.	Corrected.
Genotoxicity – Please correct: "results Ames tests were negative" (add the word "in")	Corrected.
Anti-Cancer Activity – Please indicate the concentrations at which the effects were observed. Currently, it just states the ranges of concentrations studied (0-90 μM). At what concentration were the effects statistically significantly different from the controls?	Revisions made.
Summary – As only one ingredient is included in this report, please correct "reviewed these ingredients" to "reviewed this ingredient". Please correct: "hyperplasia for the forestomach" ("for" should be "of")	Corrected.
Table 3 – In Table 3, where more details about a study should be included, please state all the concentrations that were tested. This would be especially helpful for reference 22 in which the results state that "Pyrogallol induced significant levels of chromosomal aberrations at <80 μM". What were the concentrations tested that were less than 80 μM (a similar order of magnitude, or much lower)?	Details added where available.

MARCH 2024 PANEL MEETING – RE-REVIEW CONSIDERATION

Belsito's Team Meeting – June 16, 2022

DR. BELSITO: Then we're going to pyrogallol. This is a re-review. The original review of pyrogallol was published in '91 with a conclusion safe as a cosmetic ingredient with present practice of use and concentration. There was a re-review in June of 2007, the Panel needing to await findings from a two-year NTP study. Then that re-review was somehow never completed. It's been 15 years since the initial re-review, so we're seeing it again.

The NTP study was published in 2013. Major findings were equivocal, squamous cell carcinomas in male mice and some evidence in female mice. Since that time, the EU has banned this ingredient in cosmetic products. I think we need to reopen it to look at exactly why, and particularly based upon the NTP studies. The first order is is everyone in agreement with reopening the document?

DR. SNYDER: I am.

DR. KLAASSEN: I agree.

DR. RETTIE: Yep. We've got no concentrations of use to anchor us anywhere, but that's (audio skip).

DR. SNYDER: Yeah, that was a critical issue for me. The NTP study was kind of equivocal, it was, in mice. It was negative in rats -- little difference in females versus males. Without the concentration of use, we really -- I mean, we're just -- the low dose was five milligrams per kilogram in that study. It's kind of hard to -- I think we -- yeah, I think we're just bound to see if we can't get the actual concentration of use or the other. It's listed as other. I don't even know how it's applied or where it's -- anyway.

DR. BELSITO: Well, last time we assumed the concentration of use. I mean, we're going to get to that in MIBK -- right -- is what it was last reported to be.

MS. FIUME: Yeah, because the concentration of use survey was performed, and it came back with no information.

MS. BURNETT: Right.

MS. FIUME: It would probably be a similar situation as MIBK.

MS. BURNETT: Right. We also had -- one of the previous cresol hair dyes had the same situation, one that we just finished -- can't remember -- 5-4-something.

DR. RETTIE: The text did mention that, at the time the original report was written, the maximum concentration of pyrogallol allowable in hair dyes in Europe was five percent. Is that a number we can use?

DR. BELSITO: I think we would use the last concentration that we had -- right Monice -- is what we've typically done?

MS. FIUME: I'd say we typically would. Also, in 2006, there were no uses reported. That 1989 use range can be misleading because at -- I believe, I'd have to go back and look. Christina, correct me if I'm wrong -- I'm thinking that was coming when uses were still reported to the FDA and it was a concentration range. Is that correct Christina?

MS. BURNETT: I think so. Yep.

MS. FIUME: Yeah. At what --

MS. BURNETT: Yeah, the -- I'm sorry. The original report, the maximum concentration had one product that was recorded in the range of one to five percent. It could've been one percent, or it could've been five percent. We don't know for sure.

MS. FIUME: Yeah. Once upon a time, concentrations of use were reported to FDA. They would be reported in ranges, not as actual numbers. That's what that's representing.

DR. SNYDER: I mean, Don, won't we likely go insufficient for concentration of use?

DR. BELSITO: Well, as in initial review that's what we'll do, but I don't think we're going to get it. Looking at the data we have, there's significant absorption. The NTP study, except for skin cancers, was fine. I think the major thing we're going to grapple with is the genotoxic, right -- the studies are positive and negative -- and are the squamous cells the result of chronic irritation. Is this truly a genotoxic material? Is that what we're seeing? Are we just seeing a non-genotoxic endpoint in the skin due to chronic irritation, particularly since there were no internal findings? I don't know. What do you think Paul and Curt?

DR. SNYDER: Yeah, I think you summarized it perfectly. The absence of positive in the rats, the genotox data, the weight of evidence would suggest this is not a genotoxic compound. It's a local irritation and cytotoxicity and proliferation. I fully agree with that interpretation.

DR. BELSITO: Yeah, because, I mean, it has the anti-tumor effect in (inaudible).

DR. SNYDER: Exactly. Exactly. Yeah.

DR. BELSITO: I don't know. We'll have to reopen it and see what's going on. I'm having a hard time coming up with reasons to ban it. But we're missing a concentration, and we don't even know what kind of product it's used in. We do know that it was a sensitizer, an irritant, based upon the LLNA. Do we have adequate sensitization data here to cover up to five percent? Then, this would be exempt from sensitization because it's a hair dye product?

MS. BURNETT: Yep.

DR. BELSITO: Yeah. Okay. Any other thoughts here, I mean, other than we're going to reopen it? At this point, the only data we need, I think, is do we have the irritation to cover five percent. Skin irritation --

DR. SNYDER: There's quite a bit of irritation --

DR. BELSITO: Yeah.

DR. SNYDER: -- if you look at the table on page 3 of 47. There's some dermal, in vitro, animal, animal, QSAR.

DR. BELSITO: What page, Paul?

DR. SNYDER: Three of 47 on the PDF, the table, this new data.

DR. BELSITO: Okay. This is really annoying that I'm not seeing my page numbers here.

MS. FIUME: Don, I don't -- it took me a while. If it's the new Adobe, there's a little box, in mine, on the very right tool bar that shows pages. I don't remember if I had to add it or if it finally started showing up there.

DR. BELSITO: Okay.

MS. BURNETT: Right, lower quadrant.

DR. RETTIE: Paul, are you on PDF 43? That's a list of references on my PDF.

DR. SNYDER: Page 3. Page 3. Page 3.

DR. KLAASSEN: Oh, page 3.

DR. RETTIE: Oh, page 3.

DR. SNYDER: It's notable new data.

DR. BELSITO: Oh, yeah, I see it, Monice, thank you.

MS. FIUME: Uh-huh. It took me forever to find it. I was a little frustrated with the new Adobe.

DR. BELSITO: Right. Okay. It looks like for new data --

DR. SNYDER: I know on the right it has the old data from the previous data. There was a slight skin irritation in the animal studies in the original assessment.

DR. BELSITO: Right. Equivocal results in animal sensitization.

DR. SNYDER: That's why I love these tables like this, to let the staff know. I really like these tables when you -- how it differs from the previous data. That's really easy for us to look at.

MS. BURNETT: Okay.

MS. FIUME: Thank you.

DR. BELSITO: I mean, is irritation an issue? Because right now, with the new data, it looks like we don't have a non-irritant concentration, right?

DR. SNYDER: Well, that mouse ear swelling's at 0.15 percent.

DR. BELSITO: Yeah. I don't know that we've -- is irritation an issue with hair dye material?

MS. FIUME: Christina, you know -- you're our hair dye expert. Do we normally call out irritation? Or would that --

MS. BURNETT: No, we usually -- I mean, the sensitization is usually exempt, but not the irritation.

DR. BELSITO: Okay.

MS. FIUME: I don't know if we've ever had a hair dye, when formulated, to be non-irritating conclusion.

MS. BURNETT: Yeah, that would be a new one.

MS. FIUME: We'd have to look back and see.

DR. BELSITO: Yeah. In the old report, for skin irritation, we had six Dunkin Hartley female guinea pigs tested with 500 milligrams per kilogram -- or 500 milligrams per/ml, rather -- which is, if I'm correct, that's 50 percent, right? Applied to two sides of the back of each animal, four patches, da-da-da-dah. The skin was assessed. There was only very slight erythema at one site. That's sort of against everything else we see, such a high concentration. There was, well, I guess, dryness and thickening leading to flaking in the skin were observed at all treated sites. This is PDF page 16 of 47.

Then there was test substance in powder was applied to a (inaudible) skin -- wasn't irritating. I'm not sure that's a very good irritation test just to put it on powder on the skin. Thoughts? I mean, I guess it --

DR. SNYDER: Well, I think it's definitely an irritant.

DR. BELSITO: Yeah. I mean, so I guess looking at what we have here, we're going to reopen. The question is concentration of use and irritation data at concentration of use that is reported up to five percent -- that is previously reported. Other thoughts? Is there any other data that we need with this reopening?

DR. SNYDER: I didn't have any.

DR. RETTIE: Nah, it seems to cover it for me.

DR. KLAASSEN: No.

DR. SNYDER: I mean, it's like classic toxicologies, Curt. It's exposure, all about exposure, right?

DR. KLAASSEN: It's always the bottom line, isn't it?

DR. SNYDER: Yeah, without the concentration of use, we're kind of stuck.

DR. BELSITO: I think, Paul, what we're going to end up having to do is assume it could be used up to five percent, which is --

DR. SNYDER: Yeah. I agree. Yeah.

MS. FIUME: Just to clarify for the announcement coming out of this meeting, it will primarily focus on the fact that this was reopened. We can probably include a note that these were some of the issues of concern going forward. We won't be able to do a formal request for data, but we can sort of include an idea of what some of the concerns were.

DR. BELSITO: Right, or maybe just a heads-up to industry.

MS. FIUME: Mm-hmm.

DR. BELSITO: Hopefully (audio skip) this report along. I mean, it doesn't really look like we're going to get much support for pyrogallol. I think that the expert Panel has always felt we have to go on science.

MS. FIUME: Yeah.

DR. BELSITO: Okay. Any other comments on this? If not, we'll move to dibutyl phthalate.

Cohen's Team Meeting – March 28, 2024

DR. COHEN: Okay. Pyrogallol. I think -- is that how you pronounce it?

MS. BURNETT: Pyrogallol.

DR. COHEN: Pyrogallol?

DR. ROSS: Pyrogallol?

MS. BURNETT: That's how we've been calling it in the office.

DR. BERGFELD: Pyrogallol.

DR. COHEN: Yeah, there's no accents for my assistance here. So pyrogallol was published in 1991 with the conclusion as safe as used as a cosmetic ingredient and it's been more than 15 years. A re-review was subsequently tabled in 2007 to await an NTP two-year carcinogenicity study. However, the re-review was not completed. We have comments on the NTP study that we could discuss afterwards.

At the time of the original report, the max concentration allowed in hair dyes in Europe was five percent, however European's now categorize this as Annex II and it's prohibited in cosmetic products. In 2006, it was reported in 11 hair dye formulations, however no concentrations were reported to the counsel in 2006 survey. In 2023 the VCRP had its use in one, quote, other hair dye product with no concentration reported. There's lots of new data, new absorption data, we have the NTP data, we have some sensitization data in mice and the question is to open or not open.

I would like Tom here to just comment on the NTP study but I'm sure the rest of you can comment on it as well.

DR. HELDRETH: Yeah. I've been communicating with Tom trying to get him back in but he's not even writing me back at this point. So, I don't know.

DR. COHEN: Can we call his cell?

DR. HELDRETH: I'll give it another try. So far that hasn't worked.

DR. COHEN: Okay. Susan, do you want to open or not open?

DR. TILTON: I was leaning towards reopening to consider the NTP study and also the Annex II listing by the E.U. along with some of the additional genotoxicity data and also, I guess, with the idea that we might get more information about use and concentration of use.

DR. COHEN: How would we get more information if we have 2023 VCRP data unless we had an IDA specifically calling for additional information? I don't know. What mechanism would we get more use data?

DR. TILTON: I don't know.

DR. COHEN: Look, my issue is, I came to the same conclusion, Susan, that we have enough data to reopen, and I'm exasperated by the fact that we're reopening this for one use.

DR. ROSS: Exactly.

DR. TILTON: With no reported concentration.

DR. ROSS: Exactly my comment. It's a lot of work but I don't think we've got any option because the previous re-review wasn't completed. We've got a new carcinogenicity data, a new mutagenicity data, new skin sensitization data, and we've got Annex II. So, yeah, reopen.

DR. COHEN: Yeah. It's a ton of -- yeah, okay. We all came to the same conclusion to reopen but it's an awful lot of work for something that we don't even know if it's being used or not. That means we have one and maybe that's the case. Okay. Bart, any comments on this?

DR. HELDRETH: Well, I mean, as we're on the precipice of seeing what we get from Cosmetics Direct, if we say reopen this we can hold off until we see what data would come from Cosmetics Direct and maybe there will be reported uses.

DR. COHEN: I love that approach. The issue is it's been a very long interval between evaluation of this. So.

DR. HELDRETH: It has.

DR. COHEN: Let's reopen it and then see how quickly the data rolls in but perhaps we can prioritize looking at the Cosmetics Direct data for this one to see.

DR. HELDRETH: We can do that.

Full Panel Meeting – March 29, 2024

DR. COHEN: So, pyrogallol was published in 1991, with a conclusion of safe as used as a cosmetic ingredient. It had been at least 15 years, and the re-review was tabled in June of 2007, with the Panel awaiting the NTP two-year carcinogenicity study. The re-review was not completed and now we are coming back to look at this for reevaluation. At the time of the original report, max concentration allowed in hair dye in Europe was five percent. However, the EU now categorizes this as an Annex II, and we have no concentration of use, and we have one reported use in other hair dye products.

There's a lot of new data here, absorption data, we have the NTP data, we have some sensitization and irritation data. And frankly, we went back and forth on this. There's a lot of data here suggesting that we should reopen it despite the fact that there's only one use. That's the motion. The motion is to reopen.

DR. BELSITO: Second.

DR. BERGFELD: Any further discussion?

DR. BELSITO: Yeah. In looking at this, just to give a heads-up to industry, we thought that first of all, in terms of the carcinogenicity studies we felt that it was not genotoxic but the effects that we were seeing were probably a result of irritation. But we did feel that we would need concentration of use and irritation up to the presumed concentration of five percent if we were to go and find this material safe as it was previously reported to be used.

But that's just a heads-up since it's just a decision to reopen at this point and not an actual evaluation of the materials.

DR. BERGFELD: All right. I'm going to call the question. The motion is to reopen. All those against? Abstaining? Unanimously accepted.

DECEMBER 2024 PANEL MEETING – DRAFT AMENDED REPORT

Belsito's Team Meeting – December 2, 2024

DR. BELSITO: Then I guess we move onto pyrogallol. Okay, so the original review of pyrogallol was published in '91 with a conclusion that it's safe as a cosmetic ingredient in the present practice of use and concentration. The re-review was tabled in June of 2007 to await findings of the NTP two-year carcinogenicity data and then just forgotten about for reasons that I don't know. And in March of 2024, since it's been at least 15 years since the initial re-review, it was brought up for re-review with the NTP study results and additional relevant studies that had been published since the Panel's last review.

We reopened the safety assessment to incorporate the findings of the NTP and the additional relevant data and finally publish the amended re-review. The Panel advised that the current use/frequency of use and concentration data and dermal irritation test data add up to the previously reported maximum use concentration of five percent were needed to aid the Panel in determining a potentially revised conclusion. There's new data that's been incorporated into the existing 2007 report and the data from 1991 report are in italics.

So, that's where we are here. It is used in eye products. Eye makeup preparations, manicuring preparations, and hair coloring preparations and we don't have use concentrations for those categories. And we have a dermal teratogenicity study from an old report. I have several from the old reports. There was also one that wasn't brought in here that is not terribly different I don't think. And the question is there's carcinogenicity but I'm not sure that it's genotoxic.

I thought the carcinogenic effects that were being described were due to chronic irritation and inflammation, but I'm interested in the Panel's thought. It would be nice to have Dr. Sam Cohen's impression on this.

DR. RETTIE: Sure. So, the carcinogenicity was mixed. It was carcinogenic in female mice and may have caused tumors in male mice, but it wasn't carcinogenic in rats, so we had this species difference.

DR. BELSITO: Okay, so you are comfortable saying that -- what about the carcinogenicity? I was just comfortable in writing it off in the discussion as non-genotoxic secondary to chronic irritation or inflammation but I'm curious how you would deal with it. I mean, because why believe one species and not another?

DR. RETTIE: Right, right. Yeah, maybe just not draw attention to that. Again, the genotoxicity was mixed but I have a note that says it was typically not an issue when tested in formulation. I guess I didn't have a lot of concerns about it. What'd you guys think?

DR. KLAASSEN: Well, I'm not tremendously positive that we shouldn't be concerned about it. Let's put it that way. You know, in general with carcinogenicity testing, generally if it's positive in one species and not in the other species it's still considered carcinogenic, and the mutagenicity isn't very clean. And, yeah, I don't know. Paul, what do you think?

DR. SNYDER: Well, on page 27 I think we have a good discussion regarding the two-year dermal carcinogenicity study and NTP in mice and rats and the promotion study data and they all basically say it was equivocal evidence and to what Don said, if it's all secondary to inflammation. I think the bigger issue for me was the original report had a maximum concentration of use was five percent. I think it was 0.1 to 5 percent and the new data we have, we don't have concentration of use, so we don't know what the max concentration of use is, right Don?

DR. BELSITO: Yeah. I mean, I have an insufficiency here for use concentration in leave on, especially those about the eye, and rinse offs.

DR. SNYDER: I totally agree with that.

DR. KLAASSEN: Carol has her hand up.

DR. EISENMANN: I just wanted to point out, to me the biggest thing about the original review was for the use of this in hair dyes and now I don't think it's used in hair dyes.

DR. BELSITO: Right. It's used in nails and eye preparations.

DR. EISENMANN: Right and the hair dye thing is this new product category. Eyelash and eyebrow dyes and the eye area product is this new product categories false eyelashes and eyelash and brow adhesives. So, it's totally different uses than what you reviewed it before.

DR. BELSITO: I understand, but our purview card --

DR. EISENMANN: And I haven't been able to get concentration of use -- I mean, I need to do a new survey, actually, because I haven't included those categories for this ingredient. But I don't think I'm going to get any data because I'm not sure we have anybody that makes the false eyelashes and eyelash and eyebrow adhesives. That's going to be the problem.

DR. BELSITO: Then we'll be insufficient.

DR. SNYDER: Insufficiency, yeah. Because original use is different now.

DR. BELSITO: There are new uses, but we can't just say, well, before it was hair dye only, now there are new uses so it's insufficient. I mean, we have more unsafe or whatever. I mean, it's possible that it's safe but before we can conclude that we need concentration of use in the different categories. I mean, that's my insufficiency.

DR. SNYDER: And I agree with that, Don.

DR. BELSITO: So, use concentration in the various categories for leave on, especially eye and rinse off. We don't even have the rinse off concentrations because it is used in one hair coloring, right?

DR. EISENMANN: FDA includes the eyelash and eyebrow dyes in the hair coloring category. I think that's what it is.

DR. BELSITO: Okay. But we don't know.

MS. KOWCZ: Carol, I have to agree. This is Alex, Don. I think I have to agree this is not in hair dyes. This is in new categories, the eyelash and eyebrow piece, so it's not an actual hair dye. Not for what you reviewed.

DR. EISENMANN: And I looked at the other ingredients in there and it didn't seem -- in the eyelash and eyebrow dyes both included iron oxides, so that is a permitted colorant in eye area products so I'm not sure it's a traditional like oxidative dye type dyes, but I don't know for sure.

MS. BURNETT: Based on the chemistry wouldn't it be a --

MS. KOWCZ: We don't know how that's used, Christina.

MS. BURNETT: Yeah.

DR. HELDRETH: Yeah. I mean, it could be used if combined with, you know, the right other reagents it could be used as an oxidative hair dye but technically --

MS. KOWCZ: You would not be the only one and in those products, Bart, that's mentioned it's both of the products that were in the FDA piece, they also used iron oxide so.

DR. HELDRETH: Yeah, yeah.

DR. EISENMANN: Which I thought was interesting that you're allowed to use iron material and pyrogallol to dye sutures. I don't know if it's that similar reaction that you're using there rather than the more traditional hair dye reaction. I don't know the chemistry.

DR. BELSITO: Okay.

DR. HELDRETH: Yeah, if I had made a wild guess on the chemistry, I would say pyrogallol could act as a chelating agent around an iron source. So, Carol, you're saying that you need to do new survey. I know that those typically take more than the three months between panel meetings. Do you think it would be appropriate for the Panel to wait for this to come back for more than one meeting? In other words, not come back in March but come back no sooner than June so that there's time for the survey?

DR. EISENMANN: Yes, that would probably be a good idea to delay it to see if I can find -- I want to try and reach out to more companies but I'm just not having much success getting responses from companies beyond our members.

DR. BELSITO: Yeah, I mean, this may be marketed by companies that -- well, I guess, they would have to report to MoCRA. So they're making more than whatever that minimum annual is, but I mean they're probably not members. But I mean I think we need to at least attempt to get that information. Christina, on PDF page 20 this was brought in from a prior report on sub chronic toxicity studies. It's just a sentence that says, "Statistically significant differences in clinical chemistry and hematologic values were observed between treatment in control groups." Do we know what those differences were?

MS. BURNETT: Let me take a look at the original.

DR. BELSITO: Yeah, I did. The original in our original report, it said the same thing, never delineated what the differences were.

MS. BURNETT: I'd have to see if I can find that original citation. We don't keep the original published data for these. This is a Burnett 1976. I'll see if I can track that down.

DR. BELSITO: Yeah. Also, in the developmental and reproductive toxicity studies there's one from the original report which is reference 43 in the original report that was not brought into this report.

MS. BURNETT: Sorry? The data wasn't brought in?

DR. BELSITO: Yeah, I mean it wasn't summarized. There's one additional DART study --

MS. BURNETT: The same reference? Okay.

DR. BELSITO: -- that's not brought over from the original report, and it was the one from reference 43 in the original.

MS. BURNETT: Okay.

DR. BELSITO: It doesn't add anything significantly but except to --

MS. BURNETT: Okay. I will go look for that because that's the same reference. Yeah, it's the Burnett 1976.

DR. BELSITO: And then with the carcinogenicity studies on PDF page 22, one, two, the third paragraph under carcinogenicity studies and it's two, four, six, seventh line down where it says, "The incidence of squamous cell carcinomas," I presume these are squamous cell carcinomas of the skin. I think it's critical to state that because you can have squamous cell carcinomas of the lung, of the uterus, of other organs. And it was really, in my estimation, a local effect of the inflammation that's going on in the skin with application of this material and not a genotoxic carcinogenicity.

MS. BURNETT: Okay.

DR. BELSITO: And following down, the incidents of inflammation fibrosis and pigmentation -- again that was of the skin.

MS. BURNETT: Okay.

DR. BELSITO: On PDF page 23, the top paragraph there, the fifth line down it says there was, "evidence of hyperplasia of the mammary gland was significantly increased compared to those of control. Additionally, the incidents of hematopoietic cell proliferation of the adrenal cortex in the incidence of" -- something's missing there. The incidence of what in the 75 milligram per kilogram female dose.

MS. BURNETT: Okay.

DR. KLAASSEN: In the hepatotoxicity section on page 25, right in the middle it says that the -- oh. Yeah, okay. "The serum AST and ALT increased to 350 compared to 208 in control animals." I guess I assume that you didn't transpose that but those numbers -- control should be about 20, not 200.

MS. BURNETT: Okay, I'll check the values.

DR. KLAASSEN: Double check that. It makes it kind of questionable when they have such high values in their control animals. I suspect it's their problem, not yours.

MS. BURNETT: Okay. But I will check.

DR. RETTIE: On PDF 18, chemical properties. I guess the chemistry here is pretty interesting. It's a superoxide reactive oxygen generator. And I think it correctly says it also generates hydroxyl radical and eventually that would be hydrogen peroxide, but I think overall it consumes hydrogen peroxide, and I thought maybe that last sentence could be just struck. The Haber-Weiss reaction piece and just leave it as pyrogallol is a potent generator of superoxide anion and other reactive oxygen species. You might add that.

MS. BURNETT: Okay.

DR. RETTIE: Yeah, there's a lot going on with this molecule. Especially when you add iron, you've got a lot of chemistry happening.

DR. KLAASSEN: Yeah.

DR. BELSITO: Christina, on PDF page 23 under co-carcinogenicity, the dermal study. The last sentence, again, developed squamous cell carcinomas of the skin.

MS. BURNETT: Okay.

DR. BELSITO: And on PDF page 25 under dermal irritation and sensitization, the data for the new studies, line one, two -- eight, nine. Where it says, "However, a significant increase in the percent ear swelling was observed in mice included with five percent" -- I think you mean, induced with five percent.

MS. BURNETT: I'm sorry, I'm still looking for where you were.

DR. BELSITO: Yeah. The new study that we have pyrogallol, two, four, six, the eighth line. "However, a significant increase in percent ear swelling was observed in mice induced with five percent," not included.

MS. BURNETT: Okay. Yes, I see that.

DR. RETTIE: On PDF 19 under non-cosmetic uses, the last sentence refers to catgut sutures. Are we allowed to use catgut in the U.S.? It's banned in a whole lot of other countries. I would've thought it would've been replaced by now by something else, but I don't know the --

DR. BELSITO: It's still used.

DR. RETTIE: Still used?

DR. BELSITO: Still used. Okay, so then in the discussion, Christina, I think we need to discuss the irritation as the likely cause for the squamous cell carcinomas of the skin and papilloma's that were observed in the NTP study. There is negative DART data that would support the use, but there's also sensitization and irritation with this material and now given the non-hair use in order to assess the safety we would need the concentration to determine that risk. So, our conclusion is insufficient for use concentration leave ons, especially the eye, and rinse offs.

MS. BURNETT: Okay, this is going out as an IDA, correct, this is the --

DR. BELSITO: Yes.

MS. BURNETT: Okay.

DR. BELSITO: Paul, Curt, Allan, anything else?

DR. SNYDER: I have nothing.

DR. KLAASSEN: No.

DR. RETTIE: Nope.

DR. BELSITO: Okay, great. So, we're all straight with this, Christina?

MS. BURNETT: Yes.

DR. BELSITO: Okay, wonderful.

Cohen's Team Meeting – December 2, 2024

DR. COHEN: Okay. So, we have, is it pyrogallol or pyrogallol.

DR. ROSS: I say pyrogallol.

DR. COHEN: Okay. Right. So, this is reported to function as a hair colorant and a fragrance ingredient in cosmetic products. As a draft amended report on pyrogallol and the original review was published in 1991 with a conclusion that it was safe as a cosmetic ingredient in present practices and concentration. A re-review was subsequently tabled at the June 2007 panel meeting to await NTP two-year carcinogenicity study.

In March, since it had been at least 15 years since the initial re-review was presented, we are presented with the NTP study results that have become available since the Panel's last re-review. The current use, frequency, and concentration data, dermal irritation test data up to the previously reported maximum use concentration of five percent are needed to help us in this revised conclusion. Since the March meeting there's no new unpublished data. RLD has it in 19 formulations in eye makeup preps, manicuring preparations, and hair coloring preparations.

Maximum use is less than 0.1 percent to five percent in hair dyes and color. However, no uses were reported by the Council in surveys conducted in 2006 and 2023. So, do I have that right? That max concentration is from the past.

MS. BURNETT: Correct.

DR. COHEN: Yeah, I just wanted to make sure. I'd like comments on the impurities section, and this has been predicted to be a sensitizer in their reports of sensitization. So, I can open it up for comments. There's also some genotox and co-carcinogenicity with benzopyrene and I don't know how relevant that'll be but what are the Panel's thoughts on this? Susan?

DR. TILTON: We don't have a concentration of use.

DR. COHEN: We don't? I don't think we're going to get one either because they did a 2023 survey.

DR. TILTON: It makes it difficult to evaluate the concerns with the dermal irritation and sensitization.

DR. ROSS: Correct. I mean, you have to ask for concentration of use again. You can't do a toxicological assessment really when you don't have concentrations of use.

DR. COHEN: Just a quick question. Is this a hair dye and nothing else?

MS. BURNETT: Unclear because some of the uses are now reported in false eyelashes/eyelash glues. The question came up in the other team. We don't know what it's actually being used as but the use as a hair dye has diminished.

DR. COHEN: Right, because if it's predicted to be a sensitizer there are reports on sensitizations of the thing and we have this collar of concentration of use of 0.1 to five percent, we have to anchor on the five percent, right? So, if it's not a hair dye, because this could be easier if this was a hair dye, right? It would just fall under that whole -- right? It's a sensitizer like other hair dyes and you're supposed to patch test before using it and there is even that comment about the coal tar hair dyes in this report, right?

So, if we're not doing this as a hair dye then we have other needs then, right?

DR. ROSS: We do.

MS. BURNETT: The past uses indicate that it was used as a hair dye.

DR. ROSS: And Christina, you said the other possible uses were --

MS. BURNETT: So, the RLD reports uses in false eyelashes and eyelash/eyebrow adhesives/glues. It also has reported uses in nail polish and enamels and it does say it has uses for eyelash and eyebrow dyes. So, it does fall under the hair coloring preparations category but not as a hair dye and color.

DR. COHEN: Right. It's not an approved use of a hair dye but it's a hair dye.

DR. BERGFELD: Can you go not supported for hair dye and get rid of all these other preparation and say not approved?

DR. COHEN: What -- you mean approved as a hair dye but use not supported --

DR. BERGFELD: Well, I'm just saying it's not used as a hair dye anymore. It first came on the market as a hair dye.

DR. COHEN: Is it not a hair dye at all?

DR. ROSS: RLD had 18 uses, right -- 19 uses?

MS. BURNETT: The RLD had 19. The VCRP reported one and the previous VCRP data had reported it in the hair dyes and colors category as recently as 2006.

MS. FIUME: And we all know Bart's feeling on reported functions, but reported functions currently in the dictionary are hair colorant and a fragrance ingredient.

DR. COHEN: But we don't usually adjudicate fragrances, right?

MS. FIUME: Well, we won't review fragrances if they have a monograph under RIFM.

MS. BURNETT: Right.

MS. FIUME: We don't.

MS. BURNETT: And it's not solely used as a -- or reported as a fragrance.

MS. FIUME: As a fragrance. Right. But that's just seems to be a new function which seems strange addition.

MS. BURNETT: And this also was banned in Europe so I don't know how much data we're going to get.

DR. COHEN: So, if it's used as a hair dye it's one way. If it's not used as a hair dye, we already know it's a sensitizer. So, if we don't have concentration of use you actually can't adjudicate. This isn't a botanical where we say formulate to not be sensitizing.

MS. BURNETT: Correct.

DR. COHEN: Right? So, how is it possible to proceed any further with this?

MS. BURNETT: We can --

DR. BERGFELD: Request.

MS. BURNETT: Yeah.

DR. COHEN: Just issue an IDA with all the data needs, right?

MS. BURNETT: Correct. Yep.

DR. ROSS: All right. Let's do it.

DR. COHEN: Okay. Let me get to that section in my --

DR. ROSS: I think Wilma had a good suggestion earlier, though. Wilma, you said just do use not supported, right?

DR. BERGFELD: Right.

DR. COHEN: Yeah, but again, it's process. You don't do use not supported if you haven't asked for the data yet and then you have -- you can do that when you ask for the data and you don't get it, or it's not being used. But it's being used.

DR. BERGFELD: Being used as a non-hair dye though. It's in makeup preparations.

MS. FIUME: You can evaluate whether the existing data are enough to tell you that it's unsafe for certain uses because use not supported is for ingredients that don't have any use. For those that have use it's safe, safe with qualifications, insufficient, and unsafe.

DR. ROSS: But the problem, Monice, it's hard to determine it's unsafe if we don't have concentrations of use. You know, it's sort of this catch-22.

DR. COHEN: Yeah, what if 0.01 percent in the sense that it -- you know, and the HRIPT's are all negative at 0.01 percent.

DR. ROSS: Yeah. I mean, I think if you want to list insufficiencies, obviously concentration of use as Susan just said. It's clearly a skin irritant at greater than 0.125 percent so we need evidence of lack of skin irritancy at whatever the max concentration is. It's a skin sensitizer at greater than/equal to 0.5 percent. There's some discussion of whether 0.5 percent is a positive or a negative but it's about 0.5 percent. So, we'd need evidence of that.

DR. COHEN: We need irritation and sensitization at max use not in hair dye, right?

DR. ROSS: Yeah. And we need ocular. It's an irritant at neat. It's okay at one percent but depending on the max concentration additional evidence in vitro of lack of ocular irritation at max concentration may be needed. And until we --

MS. FIUME: So, David, further than the animal ocular irritations not sufficient. Is that what you just said?

DR. ROSS: Well, we don't know what the concentration is. And so, if it's one percent that's great.

MS. FIUME: It was tested neat.

DR. ROSS: Yeah, it was tested neat. It was an irritant. Ocular irritant. It was okay at one percent.

MS. FIUME: Oh, I'm sorry. I read it as -- I was reading the next sentence where it was not -- okay, I'm sorry. I was confusing the two sentences. I was combining them in my head. Sorry about that.

DR. ROSS: No. It's often me that gets it wrong but I'm just reading my notes here. I'm not looking at the dossier but, yeah, irritant at neat -- okay at one percent. So, depending on the max use we might require additional evidence to clear the ocular use. If it's used at five, ten percent or whatever, we don't know. Well, five percent max.

MS. BURNETT: Especially since it's being reported use around the eye.

MS. FIUME: I combined the two sentences. I read the first part where it was tested undiluted and the second part that said not irritating and combine them into one. Sorry, that was my mistake.

DR. COHEN: What about the co-carcinogenicity issue?

DR. ROSS: I didn't raise a flag on that.

DR. TILTON: It's not genotoxic.

DR. COHEN: But these mice seem to develop squamous cell carcinomas when they were co-stimulated with benzopyrene and pyrogallol.

DR. BERGFELD: They're carcinogens.

DR. ROSS: Yeah, whenever you put benzopyrene in the mix though you've got --

DR. COHEN: Right, but wasn't it more than --

DR. ROSS: Is it more than the actual -- yeah.

DR. COHEN: Yeah, no. It was three times more than just the benzopyrene.

DR. ROSS: Have a look at that.

DR. TILTON: Likely due to irritation or inflammatory type mechanisms. But not as a genotoxic chemical.

DR. ROSS: Yeah, it's kind of -- the service it does pop out at you but I'm not sure it's that easy to interpret. Susan just pointed out that --

DR. COHEN: No. It speaks to smoking or other exposures to benzopyrene and environment and then having this on your face.

DR. ROSS: Well, we certainly highlight that. I think we discussed last time the carcinogenic activity was noted in one species at the treatment site and in one gender and we discussed whether it was probably related to hyperplasia inflammation at the application site. But, whatever. That needs to be in the discussion and maybe the co-carcinogenicity needs to be in there also.

DR. COHEN: Yeah. I'd like that. So, I have concentration of use, irritation and sensitization at max use not used in hair dye, ocular irritation at max use near the eye. What else do we need?

DR. ROSS: That covers my summary, I think.

DR. TILTON: Yes, I agree.

DR. COHEN: Okay. I present this so we'll go as an IDA and then we'll just see how the data plays out on that because we don't think this is just a hair dye. Great. Any other comments, questions, or concerns about this?

DR. BERGFELD: So, are you going to be selling it as a hair colorant or just a colorant?

DR. COHEN: No, I'm going to call it as an IDA with these uses and have a discussion about clearing this as a hair dye only if we don't get any of that information and have unsafe for the rest of the uses.

DR. BERGFELD: Okay.

DR. COHEN: Does that make sense?

DR. BERGFELD: Yeah.

DR. COHEN: All right, so that would just be a split conclusion. But that conclusion, ironically, would be anchored to the use reports and we usually don't do that, right? It would be from the RLD. That's why we're doing it.

MS. FIUME: So, Christina, recently we've had several hair dyes that have also reported use in nail colors as well, right, and the conclusions had to be split based on what the VCRP said. Isn't that correct?

MS. BURNETT: Well, so it was -- yeah, some that were in eye makeup or nail polish/nail products and basically the conclusion reads that -- or it's not in the conclusion, but the discussion points out that the ingredient is a coal tar hair dye, and any other uses is not approved use of a colorant. So, I guess it comes down to clarification as to what this actually is.

DR. COHEN: Right, not that many split conclusions like that but just clearing it as a hair dye and discussing its not approved uses.

MS. BURNETT: Right.

MS. FIUME: But the conclusion included both, right? Christina, is the conclusion split insufficient for other uses or was it only referring to the hair dye?

MS. BURNETT: Well, unfortunately, I'm looking back at PPD because I know that's in there but that's not a good example of it. It's not a split conclusion, no. We just cover it in the discussion that this is a hair dye, and it shouldn't be used in anything but a hair dye.

DR. BERGFELD: Under uses it declares it as a hair dye. Coal tar hair dye.

MS. BURNETT: Current language, yep.

DR. COHEN: Well, I think we got our points for tomorrow.

Full Panel Meeting – December 3, 2024

DR. COHEN: So, Pyrogallol, which is reported to function as a hair colorant and as a fragrant ingredient in cosmetic products. This is a draft amended report on Pyrogallol. The original review was published in 1991, with the conclusion that Pyrogallol is safe in cosmetic ingredient in present practices of use and concentration.

A re-review was subsequently tabled at the June 2007 Panel meeting to await the findings of an NTP two-year carcinogenicity study. In March 2024, a re-review was performed and additional relevant data became available. We reopen the safety assessment to incorporate the NTP studies and additional relevant data.

We had suggested at the time that current use frequency and concentration data, dermal irritation test data at the previous reported maximum use concentration of 5 percent are needed to help us determine a conclusion. Since the March meeting, no new, unpublished data have been received. RLD were received and have been incorporated into your report, which showed 19 uses in eye makeup preparation, manicuring preparation and hair colors. The VCRP had its use in one "other" hair color product. Max use concentration in the original safety was up to 5 percent. However, no uses were reported to the Council surveys in 2006 and 2023. It's been predicted to be a sensitizer and there are reports of sensitization.

Given that we, at this point, cannot adjudicate this solely as a hair dye, and despite reported use not typically driving our decisions since they can be erroneous or unsanctioned, our motion is an insufficient data announcement with the following needs: concentration of use, irritation and sensitization at max use. Ocular irritation at max use near the eye.

DR. BERGFELD: And that's your motion?

DR. COHEN: That's my motion.

DR. BERGFELD: Is there a second or a comment?

DR. BELSITO: I mean, I'll second it. We thought the first thing we needed was use concentration to be able to determine the safety of the other issues that David mentioned, but we're going insufficient so I'm fine with those requests as well.

DR. BERGFELD: Okay. Any other comments to be spoken about right now? If not, I'll call the question. All those for insufficient please -- those abstaining, please indicate so by raising your hand. Opposed? This is approved. All right. Thank you.

DR. BELSITO: Just one thing, Wilma, on this. We felt that the reports of squamous cell carcinoma and papillomas of the skin were not genotoxic, they were secondary to chronic irritation.

DR. BERGFELD: And would you like it --

DR. COHEN: You talking about benzo(a)pyrene co-carcinogenicity, you're talking about?

DR. BELSITO: We're talking about the NTP studies.

DR. BERGFELD: Do you want that in the Discussion?

DR. BELSITO: Yeah.

DR. BERGFELD: Okay.

DR. BELSITO: Because if it were carcinogenic, we'd be banning it, right?

DR. BERGFELD: Right, exactly. Okay. Anything else? Okay.

JUNE 2025 PANEL MEETING – DRAFT TENTATIVE AMENDED REPORT

Belsito's Team Meeting – June 9, 2025

DR. SNYDER: Moving on to the next one, Pyrogallol. Let me bring it up on my computer here. This is a Draft Tentative Amended Report. Also, in December of 2024, we issued an Insufficient Data Announcement. We had three data needs. We needed the maximum concentration of use, we needed dermal irritation and sensitization at the maximum concentration of use, and we needed ocular irritation at the maximum concentration of use.

We got updated concentration of use and there's no uses. There's no new data received. And, likewise, on Wave 2, we received some comments, largely editorial, on Page 32 of 35 of Wave 2, from PCPC. So I think we can, likewise, with this one, move it to insufficient.

DR. BELSITO: Maybe I'm hallucinating here, but I saw uses listed in the RLD, which would be adulterated uses. They weren't hair dyes. I didn't understand our request because this is supposedly a hair dye, right? And in the RLD, there were reports and uses on eyebrows and lashes. Is that not the case?

DR. SNYDER: I didn't catch that. Did anybody else have that? Christina? Yes? Okay. So we need to add that?

DR. BELSITO: Well, I mean, it's supposedly is a coal tar hair dye, right? So it shouldn't be used in anything but a hair dye. So, I guess, where do we go with this? I mean, do we have to open it to say that these uses are unapproved uses? We have no concentration of use.

DR. SNYDER: Could we put that in the Insufficient Data Announcement?

DR. BELSITO: Well, I mean, it's not that data isn't sufficient. It goes against FDA regulation, right? This is only supposed to be used as a hair dye. And not for a hair dye that's used on eyelashes or eyebrows, which I presume is what these uses on eyebrows and lashes is for.

DR. HELDRETH: Right. So this is a Draft Tentative Amended Report, and we already have data insufficiencies. So, if the data insufficiencies are the same, then it would go out as an Insufficient Data Conclusion. But if there are new insufficiencies, then you would issue an IDA at that point.

As far as these other uses, the Panel can discuss, in the report somewhere, that they feel that either these aren't safe uses or these don't fall within what's considered acceptable types of uses in there, and make that discussion point.

DR. SNYDER: So what's your preference, Bart, that we do? How do you think we should handle it?

DR. BELSITO: Well, I put insufficient for concentration of use in hair dyes and misbranded for all other uses.

DR. HELDRETH: Yeah, I mean, I don't disagree with that, but it's not up to CIR or the Panel to make a mark of misbranded or not. That falls into FDA's hands. Probably our presenter this morning would have some hand in making that call. But we can just determine if we think that that's a safe use or not, or if we want to say that it's outside of our purview.

DR. SNYDER: I think at a minimum, we have to say it's outside of our purview because it goes against our policies for coal tar. Right, Don?

DR. BELSITO: Well, it goes against the FDA policy.

DR. SNYDER: FDA, yeah, yeah, sorry, yeah, yeah. I guess we'll have a discussion on how to handle it tomorrow.

DR. HELDRETH: Yeah. I mean, in the past when we've had things like this where there's a strange use and we don't really get it, and it doesn't make sense and it's hard to say the safety about it, and especially since it's outside of our purview, typically, instead of going at it, we go around it and say, "Here's the safety as used as a hair dye."

And if you want to get very specific, like we have with some of these others in the past, where it's been a hair dye and somebody used it in some sort of an eye product, the Panel could specifically call out, "This doesn't apply to those types of uses. That's not what we mean when we say hair dye. We don't mean this hair. We just mean the hair on the top of your head.

So, I think that's historically the more common approach that the Panel has taken to a situation like this.

DR. SNYDER: Okay.

DR. BELSITO: I understand. But then let's go back to the fact that it's listed as a coal tar hair dye. Why are we asking for sensitization and irritation and ocular irritation? Because it's not supposed to be used around the eye. And we don't -- I mean, unfortunately, the FDA says that as long as you do a pre-test on it, sensitization is not an issue.

MS. BURNETT: Correct. I think the query was from the Cohen team because they wanted to address the non-hair dye uses. It wasn't specific for the hair dye use, it was the concentration of use for the non-hair dye use and sensitization and ocular irritation for non-hair dye uses, especially if it's at a different concentration.

DR. BELSITO: So are we going to try and approve this as a non-hair dye when it's listed as a coal tar hair dye? I mean, that's not our purview, right?

DR. HELDRETH: I agree. I don't think that's --

DR. SNYDER: I think we just state that it's out of our purview.

DR. HELDRETH: Right. I mean, and if we do have that data, if we do have that sensitization data, you know, the Panel could make some remarks on how that would affect the safety, but ultimately it's not going to be part of the conclusion because we're only concluding on hair dye use.

DR. SNYDER: Okay. Christina, you got that, how to word that?

MS. BURNETT: So, are you saying it is safe as a hair dye and then --

DR. BELSITO: No, we don't have a concentration of use.

DR. SNYDER: No it's insufficient.

MS. BURNETT: Insufficient? Still insufficient?

DR. SNYDER: Still insufficient.

MS. BURNETT: Okay. Insufficient for a hair dye --

DR. BELSITO: Concentration as a hair dye; and in the Discussion, point out that as a coal tar–derived hair dye, according to the 1938 FDA regs, it should not be used on eyelashes and eyebrows.

MS. BURNETT: Correct. And any other uses are not in the purview. Okay.

DR. BELSITO: Right.

DR. KLAASSEN: I have a question about the carcinogenicity. Are we not concerned about this?

DR. BELSITO: Well, we discussed this in the old Discussion. But if you look at it, it's all due to chronic severe irritation, so it's not genotoxic. It's a matter of chronic and severe irritation.

We have in vitro genotox that's positive, but the in vivo genotoxic, Curt, is negative. I mean, there are basically squamous cell carcinomas that occurred around the sites of ulceration as a result of the irritation.

DR. KLAASSEN: Yeah. Okay.

MS. BURNETT: I can add that to the Discussion, too.

DR. SNYDER: Yeah. Yeah. Perfect.

DR. BELSITO: Yeah, it was in the original Discussion. I think it was handled fairly well. There's negative DART. The 13-week dermal study was negative except for severe irritation, I mean, it's clearly an irritant.

The percutaneous absorption was fairly high, though. So the one question that I -- it was like 26 percent after 30 minutes when it was mixed with 2 percent Pyrogallol with 3 percent peroxide as the final mixture. And, Paul, there's an antithyroid effect where it's said to be more potent than PTU. What did you think of that?

DR. SNYDER: I didn't have any comment on that.

DR. BELSITO: Okay. Because that would be the only systemic effect that seemed to bother me given that absorption, because the absorption was given at 30 minutes mixed with peroxide. So it was almost like what you would expect when you were using it in a hair dye.

DR. RETTIE: Were you surprised at the amount of absorption even after it was added to peroxide?

DR. BELSITO: I was. You know, comment on it, Allan. I was surprised, but that's what we were given in the data if you look at it.

DR. RETTIE: Yeah. I mean, we've looked at other hair dyes; and then, in the presence of oxidizing agents, they all go to something else. So this is different. Of course, it's not an aromatic amine, so maybe that's part of it. We've got a lot of data on the aromatic amines, but these catechol-like things we don't. So we have to take the data as read, I guess.

DR. BELSITO: I mean, it's the data we have.

DR. KLAASSEN: Yeah.

DR. BELSITO: Okay, so we're going for insufficient for concentration of use in hair dyes, and in the Discussion point out that the in vivo genotox is negative. The carcinogenicity is presumed to be due to chronic irritation and it would not be appropriate for use on eyebrows and eyelashes for the FDA.

DR. SNYDER: Yep, perfect. You okay, Christina?

MS. BURNETT: Mm-hmm.

Cohen's Team Meeting – June 9, 2025

DR. DAVID COHEN: Okay. Pyrogallol. It's a Draft Tentative Amended Report. At the December 2024 meeting, we determined that the data were insufficient to support safety. The additional data needs are maximum concentration of use, dermal irritation and sensitization at max concentration of use for non-hair dye uses, ocular irritation data at maximum concentration of use for products used around the eye.

Since the IDA, the CIR has received an updated concentration of use survey from the Council. The survey found no uses of Pyrogallol, but suppliers indicated that Pyrogallol is a component of some plant extracts and may be found in cosmetics in low concentrations as an incidental ingredient. No other data were received.

DR. SAM COHEN: Can't we just do this on non-use and --

DR. DAVID COHEN: Well, the problem is that there -- the survey says no use, but suppliers are saying it's appearing in the cosmetic food chain use a pump, right? But it's in the chain there somewhere. So, I don't feel good about just casting it aside.

DR. SAM COHEN: Wouldn't those -- where it's found in other things, those botanicals get evaluated separately, individually, wouldn't they?

DR. ROSS: Yeah.

DR. DAVID COHEN: The botanicals would, but not the Pyrogallol.

MS. FIUME: But there are uses in the registration and listing data, so it can't go under the non-used caveat because there are reported uses to FDA.

DR. BERGFELD: So you're saying you still have to go for insufficient?

DR. ROSS: Exactly. Insufficient to evaluate safety of Pyrogallol. Same insufficiencies as previous.

DR. SAM COHEN: Some of the data in the previous review, it was brought up that there were skin tumors in the mouse study, and it was attributed to inflammation, but I'm not sure you can do that because there's a lot of positive genotox.

DR. DAVID COHEN: Oh no, that wasn't in the IDA before.

DR. SAM COHEN: No, but I'm just saying, in reviewing the carc data and genotox, I'm not sure that you can attribute it to the inflammation. And that it could be due to genotoxicity.

DR. BERGFELD: Would that be detailed in the NTP report we're waiting on?

DR. SAM COHEN: I don't know.

MS. FIUME: Or is this more of a concern that was in the Discussion?

DR. SAM COHEN: It'd be in the Discussion. Yeah.

MS. FIUME: It's in the Discussion and not probably a valid point.

DR. SAM COHEN: There was a lot of positive genotox results.

DR. TILTON: In vitro, right? Not in vivo?

DR. SAM COHEN: Yeah. But you don't have in vivo to override it. The in vivo is micronucleus and chromosome aberration, but it doesn't override the (inaudible).

DR. DAVID COHEN: So we are continuing the IDA to an IDC. Is that right?

DR. BERGFELD: Yep.

DR. ROSS: Yep.

DR. DAVID COHEN: I don't think there's any further discussion, right?

MS. FIUME: But do you want wording change to that paragraph of the Discussion?

DR. SAM COHEN: You have to put something in there about the fact that you have positive tumorgenicity data and positive genotox.

DR. DAVID COHEN: Positive genotox for the Discussion.

DR. SAM COHEN: Including the Ames assay.

DR. DAVID COHEN: So genotox and what else?

DR. SAM COHEN: Positive genotox and positive tumorgenicity in the mouse dermal study.

MS. BURNETT: So that paragraph in the Discussion needs to be completely revised then?

DR. SAM COHEN: I think so. I don't think you can attribute it to inflammation only. Maybe a combination, but I don't think you can dismiss the genotoxicity.

MS. BURNETT: Okay.

DR. DAVID COHEN: That's why you're here. That's very important.

Full Panel Meeting – June 10, 2025

DR. SNYDER: Pyrogallol, this is a Draft Tentative Amended Report. In December of 2024, we issued an Insufficient Data Announcement. We wanted maximum concentration of use as a hair dye. We wanted dermal irritation and sensitization at maximum concentration of use, and we wanted ocular irritation, sensitization and maximum concentration of use. We got updated concentration of use, indicating there's no uses, and so no data was received. So, we would still continue with the Insufficient Data Announcement.

DR. DAVID COHEN: Second.

DR. BELSITO: No, Paul, we got uses. It's used in eyebrows and lashes.

DR. SNYDER: Right. That’s correct.

DR. BELSITO: So we don't have any legitimate uses for it as a hair dye. Again, hair dye should not be used on eyebrows and lashes.

DR. DAVID COHEN: Right. We agree.

DR. BERGFELD: It's been seconded. Are we commenting now on this?

DR. DAVID COHEN: We’re commenting. Yeah, we agree with that. I think, Sam, you might want to make a comment about the need to rewrite the Discussion regarding the genotox and tumor formation in mice.

DR. SAM COHEN: Yeah, I think that although there's a lot of evidence that the tumor formation could be due to the inflammatory and regenerative phenomenon, the fact that there's a lot of positive genotox data here, you couldn't exclude A genotoxic mode of action, more likely it's a combination of the two. Even though it's very weak it's based on a dermal application. So I think that would have to be included in the write up.

DR. BELSITO: But the in vivo genotox was all negative. It was just the in vitro.

DR. SNYDER: That's correct.

DR. SAM COHEN: Yeah. But the in vivo was a micronucleus and that wouldn't override an Ames assay. It would only override an in vitro micronucleus and maybe a chromosome aberration.

DR. BELSITO: So we need additional in vivo data?

DR. SAM COHEN: Well, if you had in vivo, which from what I understand you can't get, you'd have to get a mutagenicity assay like a Big Blue or MEGA mouse. But without that, you'd have to make the assumption that there's still genotoxicity potential.

DR. SNYDER: Curt or Allan, any comment?

DR. SAM COHEN: I mean, barring that, you could ask for some evidence that there's actually reactivity of this compound with metabolic activation to forming DNA adducts. And if there's no evidence of DNA adducts, then one could exclude the likelihood of DNA reactivity and genotoxicity. That would be an in vitro study.

DR. RETTIE: My notes say that we have an in vivo micronucleus.

DR. BERGFELD: Can't hear you, Allan.

DR. RETTIE: My notes say we have a negative in vivo micronucleus for the 4.

DR. SAM COHEN: Yeah, there's an in vivo, but it's micronucleus; and micronucleus assay doesn't override an Ames assay.

DR. RETTIE: Okay. You're the expert.

DR. SAM COHEN: You'd have to have an in vivo mutagenesis assay like a Big Blue or one of those. But barring that, some in vitro evidence that you could use would be to see if there's any evidence of DNA reactivity in an in vitro metabolic activation system with DNA present. My guess is that there's not going to be, but right now you can't exclude the possibility of mutagenic activity.

DR. BELSITO: What about something in silico like blue screen? That wouldn't --

DR. SAM COHEN: Yeah, you could try that.

DR. BERGFELD: Curt?

DR. KLAASSEN: It does turn out that the Ames tests, while there's been a lot written about it over the last 40 years, it turns out to be superb and it's an in vitro test. You can't throw Ames tests away very easily.

DR. SAM COHEN: No, the only way you could override it would be either an in vivo mutagenesis assay like Big Blue, or some evidence -- however you generate it, whether in silico or, I just prefer in vitro -- showing that it actually doesn't interact with DNA. And my guess is just from its structure, I don't see how it's going to be activated to react with DNA, it's a triphenyl. But right now the data you have is that you can't exclude a mutagenic mode of action.

DR. BERGFELD: Okay. I think it's agreed that it's going to go out as an insufficient report. Is that correct?

DR. HELDRETH: Looking at the data needs from the previous IDA, I'm hearing new data needs. Therefore, that would mean a second IDA would be warranted instead of an insufficient data conclusion.

DR. BERGFELD: Okay. Okay.

DR. DAVID COHEN: What are the new data needs? I didn't know if I heard that same thing.

DR. SNYDER: I'm deferring to the experts.

DR. SAM COHEN: I think just some evidence that it does or doesn't react with DNA upon metabolic activation. And that if it can be generated in silico, I think that's fine, but I would prefer in vitro.

DR. ROSS: Do we need that now? I mean, I think the conclusion is insufficient, right? So it's insufficient to evaluate safety. Sam, do you need that because it would have to go out again?

DR. SAM COHEN: No, I think if the overall conclusion is that it's insufficient data, it's insufficient data and this is just another requirement.

DR. BELSITO: This is not a final. Right? So industry has the opportunity to come back to us with this. Where are we here, Bart?

DR. SNYDER: Bart stated that we'd have to go out with a second Insufficient Data Announcement, Don, because we've added an additional data need and so it has to go back out.

DR. DAVID COHEN: Right.

DR. HELDRETH: We're currently sitting on a Draft Tentative Report. If you had no new data needs then you could issue a Tentative Report with an Insufficient Data Conclusion. But to be fair to stakeholders, to give them an opportunity to submit data when you have a new data request, it's appropriate to put out a second Insufficient Data Announcement first. And so this would come back again with another, revised essentially, Draft Tentative Amended Report in the future.

DR. DAVID COHEN: Look, if we got dermal irritation and sensitization in the ocular data, would we be prepared to clear it, right? If the data needs were filled with the existing IDC right now, would we clear it?

DR. BELSITO: No.

DR. DAVID COHEN: Right. So we need a new IDA.

DR. SNYDER: Good point.

DR. BERGFELD: So you're gonna restate your motion?

DR. SNYDER: Sure. So we continue with the Insufficient Data Announcement, with the maximum concentration use as a hair dye, the dermal irritation and sensitization and maximum concentration of use, ocular irritation at maximum concentration of use, and with the addition of some data that shows that it either does or does not react with DNA. Is that correct, Sam?

DR. SAM COHEN: Yes, I think that would be perfect.

DR. SNYDER: It could be in silico or whatever.

DR. BELSITO: And clarification on this eye use.

DR. SNYDER: Yes.

DR. BERGFELD: Christina?

MS. BURNETT: I just wanted to note in one of the teams yesterday that the two insufficiency requests were for non-hair dye use, but as far as we know this is a hair dye. So if it is just being considered a hair dye, uses that are not hair dyes are considered to be outside of the purview on this. I'm questioning if that is still a data request? If you would like it, that's fine. I just want to make sure for our purposes that we have it written up correctly.

DR. BELSITO: I think, Christina, it's essentially the same thing we're asking, it's clarification about this eye use.

DR. BERGFELD: All right. Are we seconding it? Are we ready to call the question then? Okay. All those in favor of a second Insufficient Data Announcement, please indicate by raising your hand. Thank you. Unanimous.

MARCH 2026 PANEL MEETING – DRAFT TENTATIVE AMENDED REPORT

Belsito's Team Meeting – March 12, 2026

DR. BELSITO: Okay. So we're doing Pyrogallol next. At the June 2025 meeting, we issued a second insufficient data for this hair dye, asking for max concentration of use, genotox studies with metabolic activation, the test for the formation of DNA add-ons, dermal irritation and sensitization at maximum concentration of use in a non-hair dye.

Not sure why we asked for that, because as a hair dye it shouldn't be used in products that aren't hair dyes. Clarification of the type of use around the eyes. And ocular irritation at maximum concentration for use of a product around the eyes. Again, that seems sort of counterintuitive since we go on to this whole issue of this is a hair dye and shouldn't be used in those areas.

Anyway, we've not gotten any published data in terms of our needs. We did get one new paper that found upregulation of pro-apoptotic genes and proteins with downregulation of anti-apoptotic markers with Pyrogallol, but I didn't really think it added anything new that we need to consider to the report.

I thought we could go as insufficient and, again, with the comment that these really should not be being used in products that aren't hair coloring. I think the biggest issue here, because I went to the Willow report after I did this, and they do point out that Pyrogallol -- this is on PDF Page 34 -- is a component of some plant extracts and could be found in cosmetics in low concentrations of use as an incidental ingredient.

So, we're going to be going insufficient for this, and then how do we handle when there are small amounts of Pyrogallol as there are reported to be in Willow extracts? Bart?

DR. SNYDER: Well, to be consistent we've got to go insufficient, because we don't have the use, right -- data, for Pyrogallol?

DR. BELSITO: Well, we have the use data for -- oh, for Pyrogallol, I don't think it's an issue. You know, we're insufficient for all the elements that were listed, except for those that -- again, I don't think we should be asking for things like irritation and sensitization because that's not an issue if it's a hair dye, right? It's a test, we would never ban for that.

Clarification of types of use around the eyes, it shouldn't be being used there, right? Because if it's not used as a hair dye and, you know, hair dyes should not be applied to the eyelashes or eyebrows. And the ocular irritation. So, we would want maximum concentration of use and genotox. The others drop out because they're not relevant to hair dyes.

And then a point in the Discussion that these reports about use around the eyes would be whatever the word is, I think it was used -- Christina has a little section on that about inappropriate use. I forget what PDF page that's on, but I thought it was quite good.

MS. BURNETT: In the Discussion, it's PDF Page 43, last paragraph.

DR. BELSITO: Yeah, I mean, that's in the Discussion. But we shouldn't be asking for that data because it's really not relevant to how it should be being used. You know, the uses in eyelashes, adhesives and nail enamels are -- I think the word is 'misbranded' or something like that. So I thought the Discussion was good and insufficient for concentration of use and genotox, essentially.

DR. SNYDER: I second that motion.

DR. KLAASSEN: Third.

MS. BURNETT: Okay. So, going forward, remove the request for the data needs for the dermal irritation and the clarification of use on the eyes and ocular irritation from the Discussion?

DR. BELSITO: Yeah, I mean, dermal irritation and sensitization is not something we ask for a hair dye, right?

MS. BURNETT: Correct.

DR. BELSITO: Because we have that statement, and a hair dye shouldn't be used around the eyes. And as we point out in the Discussion, as you have in the Discussion, therefore, why are we asking for clarification about the use around the eyes? It shouldn't be being used there. There's no clarification needed. Right?

MS. BURNETT: Correct.

DR. SNYDER: I think we just need to clearly state that in the Discussion.

DR. BELSITO: Well, we do.

DR. SNYDER: Yeah, that's what I mean.

DR. BELSITO: Christina has that whole paragraph that these are not FDA-approved uses for a colorant.

DR. SNYDER: So, we just have two data needs: maximum concentration of use and genotox with metabolic activation.

DR. BELSITO: Right. The test formation of DNA adducts.

DR. SNYDER: I think that's it. I think we got it.

DR. BELSITO: Okay. But let -- can we get back to the Pyrogallol issue as a small component of naturals?

DR. SNYDER: Okay.

DR. BELSITO: Bart, how are we going to deal with that when we get to Willow?

DR. HELDRETH: Well, I mean, I think we have to treat it the same way we would any impurity in an ingredient. If we know that this is present, then we need to know how much, and is that amount above a threshold of concern? Or if we can't determine a threshold of concern, we would need some further statements. I think Carol might have an answer for us.

DR. EISENMANN: You're not going to get the amount because they won't keep track of them. They don't measure this. When I did the concentration of use survey for this ingredient, some people told me that it's a small component of some plants. They don't intentionally add it, they add some pla- -- and, you know, what levels of plants they add? It's very low concentrations of plant ingredients they add, and this will be a small component of that. So, you're talking about a very, very small level.

You're never going to get the amount. Are you really concerned about a very tiny amount of -- I mean, it's probably in plants we eat, too, for that matter. So, you know, it would be very hard to track. There's a lot of components in plants that you've expressed concern over the years, and you don't necessarily ask for the information on what levels there are in each plant.

DR. RETTIE: Has this come out before for this ingredient in other botanicals?

DR. EISENMANN: Not for this ingredient.

DR. BELSITO: Yeah, but on the other hand, Allan, I don't think we've ever had it bubble up into our consciousness about this Pyrogallol. I wouldn't necessarily -- I may have thought about it because, I mean, I've been on the Panel long enough that Pyrogallol has been reviewed, and I know it's not been found safe. But I can't say.

DR. RETTIE: I was just wondering if there was an easy modification to our boilerplate for botanicals that we could make.

DR. BELSITO: Well, I think we probably will need to discuss this a little bit with the entire group tomorrow, depending upon whether Willow comes up first, I don't remember, or Pyrogallol. I think Pyrogallol comes up first, no?

DR. KLAASSEN: Yes.

DR. SNYDER: Yes.

DR. HELDRETH: I think there are a couple approaches, one being what Carol suggested. If we're looking at the Willow ingredients, the highest concentration of use is 1.1 percent in a leave-on; even if all of that was Pyrogallol, is that above a threshold of concern? Maybe it is. If that's below a threshold of concern then maybe we can mitigate that issue, or maybe we can do some sort of risk analysis of how much, possibly, that could be Pyrogallol. The other possibility would be to make a determination in the Discussion that manufacturers need to limit the level of this impurity.

DR. BELSITO: Yeah, I guess the issue that I had, though, Bart, with the Pyrogallol is this isn't something like a sensitizer. The issue that we're asking for that's insufficient is genotox.

DR. HELDRETH: Right.

DR. BELSITO: And if it's genotox, you know, in the EU, it just would be outright banned in a cosmetic, right?

DR. HELDRETH: Right.

DR. BELSITO: So, the problem I had is the issue that's insufficient for this.

DR. HELDRETH: Right. Right.

DR. BELSITO: Because the EU considers there's no -- and I don't know what we consider, Curt, I'd be interested in your opinion -- but there's no safe level for a genotox material is what I've always been told.

DR. KLAASSEN: Well, you're right. And here, if it's genotoxic they kind of "ban" it, because that's considered a hazard assessment. But if you do risk assessment, you put into consideration how much you're exposed to, and it turns out in the big picture, 50 percent of the chemicals are genotoxic. And we all eat genotoxic chemicals every day in our food, in our water. So, generally in the United States, when we have genotox, then we do risk assessment. But it's a pretty conservative risk assessment, so we don't ban it like Europe generally does.

DR. BELSITO: Okay.

DR. KLAASSEN: That's actually one of the major differences between the regulations in the United States and Europe, is how we look at endocrine disruptors, how we look at genotoxic chemicals, especially those two -- or those that might cause birth defects.

Europe generally does hazard assessment on those, and if it's positive, then you kind of ban it. In the United States, we do risk -- we go to the second step. We take into consideration the dose, and then that is what's considered risk assessment rather than just hazard assessment. So, that's where I'm at.

DR. BELSITO: Well, I guess we'll have this discussion when we get to Pyrogallol and further it with Willow, as to where we're going to go.

DR. KLAASSEN: Sure.

DR. BELSITO: Okay. But otherwise, Pyrogallol is insufficient for concentration and genotox with activation. Not the others.

Cohen's Team Meeting – March 12, 2026

DR. DAVID COHEN: This was originally reviewed by the Panel in 1991, with the conclusion that it was safe as a cosmetic ingredient in the present practices of use and concentration. A re-review was initiated in 2007, but was tabled pending completion of the NTP two-year carcinogenicity study. The Safety Assessment was reopened in 2024, to incorporate the NTP findings and other newly available data.

At the December 2024 meeting, the Panel issued an Insufficient Data Announcement with many requests for information, max use, genotox with metabolic activation addressing DNA adducts, dermal irritation and sensitization at max concentration of use for non-hair dyes, clarification of the type of use around the eyes, ocular irritation at max use around the eyes. Since the issuance of the IDA, no unpublished data has been received.

The frequency of use information has been updated with the 2025, RLD, with only one additional reported use in an eye makeup preparation. It appears that the IDA is unreconciled.

DR. BERGFELD: And it's European Annex II, now, this dye?

DR. ROSS: Yeah, same as previous. Yeah.

DR. DAVID COHEN: So, is our motion an Insufficient Data Conclusion?

DR. BERGFELD: It has to be.

DR. ROSS: Yeah.

DR. SAM COHEN: Yeah.

DR. DAVID COHEN: And the requirements remain?

DR. SAM COHEN: Yeah.

DR. ROSS: Yeah, it's exactly the same, I think.

DR. DAVID COHEN: Yeah, there's no change. All right, any other comment on this?

MS. BURNETT: Was the Panel satisfied with the draft Conclusion?

DR. SAM COHEN: There was no --

MS. FIUME: Draft Discussion?

DR. SAM COHEN: Draft discussion, yeah.

MS. BURNETT: Oh, I'm sorry.

DR. ROSS: I didn't have anything in it, I don't think.

DR. BERGFELD: Yes, I was.

DR. DAVID COHEN: I didn't make any comments. I saw it, but I didn't make any comments about it.

DR. SAM COHEN: Yeah. No, I think it's fine.

MS. BURNETT: Okay. Thank you.

DR. SAM COHEN: Boy, that one went quickly.

DR. DAVID COHEN: Well, you know.

DR. ROSS: It was a big one.

DR. DAVID COHEN: Yeah, when we can go quickly, we can; when we need to pause, we pause.

DR. ROSS: Yeah.

Full Panel Meeting – March 13, 2026

DR. DAVID COHEN: Okay. Pyrogallol was originally reviewed by the Panel in 1991, with a conclusion that it was safe as used in present practices of concentration of use.

DR. BELSITO: David, I'm having trouble hearing you. Are other people?

DR. KLAASSEN: Yes.

DR. DAVID COHEN: How about now?

DR. ROSS: That's better.

DR. BELSITO: A little better.

DR. DAVID COHEN: I didn't do anything. I'll start from the beginning. Pyrogallol was originally reviewed by the Panel in 1991, with the conclusion that it was safe as a cosmetic ingredient in the present practices of use and concentration. A re-review was initiated in 2007, but was tabled pending the completion of the NTP two-year carcinogenicity study. The safety assessment was reopened in 2024, to incorporate the NTP findings and other newly available data.

At the December 2024 meeting, the Panel issued an Insufficient Data Announcement with several needs, including maximum concentration of use, genotox studies with metabolic activation, dermal irritation and sensitization at max use for non-hair dye uses, clarification of the type of use around the eyes and ocular irritation at max concentration for products used around the eyes.

Since the issuance of the IDA, no unpublished data has been received addressing these data needs. The frequency of use information is updated from the 2025 RLD. Since we have unresolved concentration of use, use around the eyes, and ambiguous non-hair uses, our motion was to continue the IDA to an Insufficient Data Conclusion.

DR. BELSITO: We're okay with that, but I think your insufficiencies are incorrect. This is a hair dye, and it's clearly stated in the cosmetic section that with regard to the reported use in eye makeup preparations and manicure preparations, the FD&C Act mandates that color additives must be approved by FDA for their intended use before they're used. Pyrogallol is not approved color additive in non-hair dye cosmetics, and therefore use in makeup products and manicure preparations is not permitted and would be considered adulterated. So, as a hair dye we don't need sensitization and irritation.

DR. DAVID COHEN: No, no, I agree with you, Don. Perhaps I wasn't clear; but these really are being driven by the non-hair dye uses.

DR. BELSITO: But that's not even in our purview. They shouldn't be used in non-hair dyes. I mean, the FDA has already said that. So, we're not -- you know, I mean, we simply state that in the Cosmetic Use section, that uses about the eye or nail enamels is not an approved use.

DR. DAVID COHEN: Well, one question is why are you okay with the Insufficient Data Conclusion?

DR. BELSITO: The Insufficient Data because we don't have --

DR. SNYDER: Concentration of use or genotox of metabolic activation.

DR. BELSITO: We don't have concentration of use or genotox. We have two insufficiencies for a hair dye, irritation and sensitization, the hair dye caveat.

DR. DAVID COHEN: I see your point. Yeah. You're suggesting that we still want concentration of use, we still want genotox?

DR. BELSITO: Right.

DR. DAVID COHEN: You don't feel you need the dermal irritation and sensitization because we're using the hair dye sort of methodology of this?

DR. BELSITO: Correct.

DR. DAVID COHEN: Even the clarification around the eyes would be unsanctioned anyway, correct?

DR. BELSITO: Yeah.

DR. DAVID COHEN: And then ocular irritation, what's your sense on that?

DR. BELSITO: I mean, again, it's a hair dye. It shouldn't be getting down into the eyes.

DR. DAVID COHEN: Yeah. Okay. So, if you guys are sort of -- we're not misaligned here, other than the IDA. The Insufficient Data Conclusion needs are maximum concentration use and genotox.

DR. BELSITO: Yeah.

DR. DAVID COHEN: Okay. It's so amended.

DR. BELSITO: Then second. Christina?

MS. BURNETT: Before we move on, I just wanted to confirm that the Discussion points that have been drafted are okay and there are no additions.

DR. DAVID COHEN: Hold on, let me look.

DR. BELSITO: Get us to the PDF.

MS. BURNETT: PDF Page 43.

DR. BELSITO: Yes, I had no additions.

DR. DAVID COHEN: But I suppose the data needs in that Discussion will change.

MS. BURNETT: Yeah. I will delete the three.

DR. DAVID COHEN: Okay. So, the motion has been made and seconded.

DR. BERGFELD: It's seconded. Yeah, I'm back on again. Sorry about all that. Although, I call the question, let's go reverse. All those opposed? Abstaining? It's approved to move on as an insufficient report.

JANUARY 9-10, 1989 PANEL MEETING

(reviewed with phloroglucinol)

Full Panel

Dr. Schroeter reviewed the data previously requested: subchronic oral study for Phloroglucinol, a UV spectra analysis for Pyrogallol and Phloroglucinol, and data on the chemistry (i.e. the ingredient concentrations that contact the skin) of Pyrogallol and Phloroglucinol in hair dye. He made the motion that an insufficient data announcement be issued in which the data be requested. After a brief discussion, the motion was approved unanimously.

JULY 24-25, 1989 MEETING

Full Panel

Dr. Bergfeld opened the discussion by noting that though two ingredients, Pyrogallol and Phloroglucinol, were listed on the report cover, only Pyrogallol was to be considered since there were insufficient data available on Phloroglucinol. She also noted that the Pyrogallol report went insufficient in January of 1989, but that the Panel had since been given new data to consider. She stated that the request for data included a UV spectral analysis, acute oral toxicity, ocular irritation, skin irritation, skin sensitization, reproductive effects, and additional co-carcinogenicity studies. The data received included animal skin irritation in the guinea pig, which was negative, and sensitization results which were mildly to moderately positive; human use data and mutagenicity data were also available. She opened the floor for discussion of the need for more data and for the acceptability of the data which had been received.

Dr. Elder noted that since Phloroglucinol had been removed from the report at the Panel's request, the 90-day study was no longer required.

Dr. Hoffman commented that the UV spectral analysis had been performed at too low of a concentration for the detection of impurities. He said that he thought it was the policy of the Panel that UV spectral analyses be performed with concentration of 1 g/l of the test material. He remarked that in the case of the Pyrogallol UV spectrum, a higher concentration of test material would not have changed the absorbance spectrum, since the analytical grade material tested was essentially pure. He noted that the Panel had developed a standard form to be sent with the data request in order to ensure that UV spectral analyses were performed satisfactorily. He reiterated his belief that all UV spectral analyses should be performed on the cosmetic grade material rather than on the analytical grade material so that if UV absorption by impurities were a potential problem, it would be detected.

On the subject of impurities, Dr. Boutwell commented that extremely small fractions of a percent of impurities such as iron are irrelevant. He noted that the Panel would have a greater concern over organic impurities which are more likely to be biologically active.

Dr. Hoffmann requested that the statement "data as to organic impurities in Pyrogallol as used in cosmetic formulations were not available" be included in the appropriate section of the Pyrogallol report.

Mr. Eiermann suggested that in the future, the Panel should specify that UV spectral analyses be performed on cosmetic grade materials. He also noted that under in-use conditions, Pyrogallol does not stay in contact with the skin for very long because it quickly reacts with other ingredients, such as p-phenylenediamine, in the formulation. He remarked that Pyrogallol did not remain in contact with the skin in its pure form but rather as a reaction product.

Dr. Hoffmann motioned that the Panel should release an insufficient data report due to lack of impurities data.

Dr. Bergfeld seconded the motion. Dr. Bergfeld then requested comments on the mutagenicity data which had been supplied to the Panel.

Dr. Hoffmann stated that he felt that it should be stated in the summary that Pyrogallol is a co-carcinogen.

Dr. Boutwell agreed with this and commented that he had great concern over co-carcinogenicity based on the Van Duuren study.

Dr. Hoffmann stated that he thought the last sentence on page 29 f the report should be changed to read: "On the skin of female ICR-HA mice, Pyrogallol is active as a co-carcinogen when applied together with benzo[a]pyrene."

Dr. Boutwell agreed with this change, stating that it was an important point.

Dr. Hoffmann then suggested that the second line on page 29 be changed to read: "Pyrogallol was mutagenic in the Ames test for the TA 98, TA 100, and TA 1537 tester strains of *S. typhimurium*."

Dr. Bergfeld commented that the sensitization data were extremely limited. She noted that since Pyrogallol is a hair dye ingredient, the concern over sensitization could be handled as it was for other hair dyes. she noted that the Panel could bring into the discussion that there is a lack of human data, and that animal data suggest lack of irritation and limited evidence of sensitization, but that since Pyrogallol is a hair dye ingredient, studies in humans would be precluded. She stated that the report should go insufficient while the question of mutagenicity should be highlighted in the discussion, as well as the UV spectral analysis and lack of impurities data.

Dr. Elder remarked that the Panel wanted to include in the discussion concerns over mutagenicity and sensitization, as well as UV absorbence and impurities, but that it was for the latter two that the report was insufficient, reflecting a lack of an adequate response to the request for phototoxicity data and UV spectral analysis.

Dr. Bergfeld asked if this would be in the discussion or the conclusion.

Dr. Elder replied that it would be stated in both, and that the lack of impurities data was one area in which the data were insufficient. He asked if the Panel wanted the discussion to include the Panel's concern with mutagenesis and co-carcinogenesis.

Dr. Hoffmann replied that a statement on mutagenesis should be included in the discussion, but that it was not necessary to include a statement on co-carcinogenesis.

Dr. Bergfeld asked Dr. Hoffmann what guidelines were followed when some mutagenicity test results were positive while other mutagenicity test results were negative.

Dr. Hoffmann replied that positive results in a standard and correctly performed mutagenicity tests would carry considerable weight.

Dr. Elder asked if the Panel would like a mail review on this report.

Dr. Bergfeld replied that she thought it was necessary in order for the Panel members to evaluate the changes made in the report. She then asked if a vote had been called.

Dr. Elder then noted that the Panel would be voting for a tentative final insufficient data report with the understanding that if the appropriate data or a commitment to perform necessary tests regrading phototoxicity and impurities were received during the 90-day comment period then the report would not go final until the new data had been evaluated by the Panel members. He then asked the Panel what advice it had concerning the impurities data.

Dr. Boutwell remarked that the impurities of major concern would be organic materials since they may be biologically active.

Dr. Hoffmann restated the Panel's desire that all UV absorption data and impurities testing be performed on the cosmetic grade material rather than on the analytical grade material.

Dr. Elder noted that this was the first time that the Panel had concluded that data were insufficient due to lack of information on impurities.

Dr. Shank called for a vote of all those in favor of a tentative final insufficient data conclusion to the Pyrogallol report. The motion carried unanimously.

NOVEMBER 13, 1989 MEETING

Full Panel

Dr. Berndt opened the discussion on Pyrogallol by referring to the Panel's action at the 24-25 July Panel Meeting, subsequent to which CIR determined that cosmetic grade Pyrogallol contained a minimum of 99.0% Pyrogallol. He suggested that the Panel rethink its request for additional data on Pyrogallol, taking into consideration the purity of the cosmetic grade product.

Dr. Hoffmann noted that in the synthesis of Pyrogallol, as in the synthesis of certain other organic compounds, the reaction may result in the formation of dibenzylpuranes and dibenzyldioxanes, which are extremely toxic. He suggested that the second sentence of the impurities section of the report should be changed to state: "data on possible organic impurities in cosmetic Pyrogallol, especially on chlorinated hydrocarbons, are not available."

Dr. McEwen suggested that wording other than especially be used, noting that though these possible impurities are of concern, they might not be the most important items of concern.

The Panel agreed and decided to reword the statement, replacing the word "especially" with "such as."

Dr. Boutwell commented that in the section on co-carcinogenicity, the VanDuren and Goldsmith study, which shows positive co-carcinogenicity when Pyrogallol together with benzo[a]pyrene was applied to the skin of mice, should be included in the discussion section of the report.

Dr. Hoffmann pointed out that the study was mentioned in the discussion, but Dr. Boutwell noted that while the facts of the study were mentioned, no analysis of the meaning or consequences of the results of the study was included. He suggested adding a sentence stating that positive co-carcinogenicity data are not to be interpreted as an indication of carcinogenesis.

The Panel agreed to the inclusion of this statement in the discussion.

Dr. Carlton suggested that a reason be given in the discussion for not requesting additional human irritation and sensitization data rather than stating that requests were precluded by the fact that Pyrogallol is a hair dye ingredient.

Dr. Berndt noted that the main reason that the Panel does not request irritation and sensitization data on hair dye ingredients is because patch testing is required before use of these ingredients.

A discussion of the Panel's action at the July meeting followed. It was noted that the Panel had previously considered the document insufficient because of a lack of data on impurities. This was compounded by the fact that the available UV spectrum for Pyrogallol was of the pure ingredient. Both of these issues were resolved when it was determined that cosmetic grade Pyrogallol was 99.0% pure.

Dr. Schroeter asked for the Panel's interpretation of the positive results that were obtained with Pyrogallol in several mutagenicity assays.

Dr. Shank noted that the ingredient had been tested, with negative results, in three adequately performed skin carcinogenicity assays, and thus in spite of the mutagenic potential of this compound, it dose not appear to be a skin carcinogen.

Dr. Hoffmann suggested adding a statement to the discussion reflecting what Dr. Shank stated. He also noted that the mutagenicity studies were not performed on pure Pyrogallol.

Dr. Boutwell noted that the multigenerational reproductive study performed on hair dyes containing Pyrogallol was also a good indicator of carcinogenic potential since the fetus is uniquely susceptible to carcinogenesis, which manifests itself first in the form of leukemia, and that although the reproductive study did not continue for a lifetime, it still indicated a lack of carcinogenic potential since young animals are particularly responsive to carcinogenesis. He suggested that this be summarized in the discussion.

Dr. Berndt asked if the Panel would like a statement in the discussion acknowledging that Pyrogallol was positive in some mutagenicity studies, but that the compound was negative in dermal carcinogenicity studies.

Dr. Bergfeld reminded the Panel that it had wanted to include in the discussion comments on the impurities and UV spectrum of Pyrogallol.

Dr. Hoffmann noted that since the Panel was now aware that the cosmetic grade Pyrogallol is 99.0% pure, the original concerns over impurities and the UV spectrum had been resolved. He noted that the Panel's conclusion would apply to 99.0% pure Pyrogallol.

Dr. Boutwell moved that the Panel amend the tentative insufficient conclusion to safe as used.

The motion was seconded by Dr. Shank.

There was a general discussion on the necessity of including in the conclusion a phrase on the purity of cosmetic grade Pyrogallol. It was decided that cosmetic grade Pyrogallol was defined in the report as 99% pure, and that the phrase "as used" indicated the cosmetic grade Pyrogallol.

Dr. Carlton asked the Panel for its opinion of the concentration of test as compared to concentration of use.

The Panel concluded that the concentrations of test were sufficient.

The Panel voted unanimously to approve a conclusion of "safe as used" for Pyrogallol.

JUNE 2007 MEETING – FIRST RE-REVIEW

Full Panel – June 5, 2007

Dr. Marks stated that a CIR Final Report with the following conclusion was published in 1991: On the basis of the available animal and clinical data presented in this report, the CIR Expert Panel concludes that Pyrogallol is safe as a cosmetic ingredient in the present practices of use and concentration.

Dr. Marks said that his Team determined that the Final Report should not be reopened for the following reasons: (1) Pyrogallol is not being used and (2) An NTP 2-year carcinogenicity study was completed, and exactly when the results of this study will be made available remains unknown. Furthermore, in the absence of results from the NTP study, it was noted that the two dermal carcinogenicity studies in the Final Report were considered by the Panel in arriving at the conclusion that was published.

Dr. Belsito said that his Team determined that it would be reasonable to table the re-review document on Pyrogallol pending the NTP study. He noted that it is expected that the results of this study will be made available in approximately five months.

Dr. Slaga said that the NTP carcinogenicity study was generated because Pyrogallol is a mutagen both in bacterial and mammalian systems. The reason for the study is also related to the fact that Itoh has published many studies on similar compounds (e.g., BHA and Resorcinol) that have an effect on the forestomach in terms of tumor formation. Another reason for the study is the fact that Pyrogallol has some activity as a tumor promoter.

Dr. Slaga said that the Panel must keep in mind that it has had studies on Pyrogallol as a complete carcinogen in the skin of mice, rats, guinea pigs, and hamsters, and all of these studies have been negative.

Dr. Slaga noted that part (subchronic dermal exposure) of the NTP study is included in the re-review document.

The Panel voted unanimously in favor of tabling the re-review document on Pyrogallol, pending availability of the NTP 2-year carcinogenicity study on Pyrogallol.

Amended Safety Assessment of Pyrogallol as Used in Cosmetics

Status:	Draft Final Amended Report for Panel Review
Release Date:	September 11, 2026
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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 Christina Burnett, M.S., Senior Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

ALT	alanine aminotransaminase
AST	aspartate aminotransaminase
CHO	Chinese hamster ovary
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CYP2E1	cytochrome P450 2E1
CYP1A2	cytochrome P450 1A2
Dictionary	*International Cosmetic Ingredient Dictionary*
DMSO	dimethyl sulfoxide
DNFB	1-fluoro-2,4-dinitrobenzene
ECHA	European Chemicals Agency
ELISA	enzyme-linked immunosorbent assay
EPA	US Environmental Protection Agency
FDA	US Food and Drug Administration
FD&C Act	Food, Drug, and Cosmetic Act
FOU	frequency of use
GIRDCA	Gruppo Italiano Riverca Dermatiti da Contatto e Ambientali
GSH	glutathione
IC_{50}	half-maximal inhibitory concentration
ICDRG	International Contact Dermatitis Research Group
LDH	lactate dehydrogenase
LLNA	local lymph node assay
MDA	malondialdehyde
MoCRA	Modernization of Cosmetics Regulation Act of 2022
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NR	not reported
NSCLC	non-small cell lung cancer
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PTU	6-*N*-propyl-2-thiouracil
qPCR	quantitative real-time polymerase chain reaction
(Q)SAR	quantitative structure–activity relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RLD	Registration and Listing Data
ROS	reactive oxygen species
SI	stimulation index
Skp2	S-phase kinase-associated protein 2
SOD	superoxide dismutase
TG	test guideline
TPO	thyroid peroxidase
US	United States

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) reassessed the safety of Pyrogallol, which is reported to function as a hair colorant and fragrance ingredient in cosmetic products. The Panel reviewed all relevant data related to this ingredient. Accordingly, the Panel issued an amended report with a revised conclusion stating that the available data are insufficient to make a determination of safety for Pyrogallol under the intended conditions of use in cosmetic formulations.

INTRODUCTION

This assessment reviews the safety of Pyrogallol as used in cosmetic formulations. According to the *International Cosmetic Ingredient Dictionary* (*Dictionary*), this ingredient is reported to function as a hair colorant and a fragrance ingredient in cosmetic products.[1] However, please note that Pyrogallol is considered a coal tar hair dye and the function as a fragrance ingredient is not appropriate for use in cosmetics.

The Expert Panel for Cosmetic Ingredient Safety (Panel) first reviewed the safety of Pyrogallol in a report published in 1991, with the conclusion "Pyrogallol is safe as a cosmetic ingredient in the present practices of use and concentration."[2] A re-review was initiated in 2007,[3] but it was tabled at the June 2007 Panel meeting to await the findings of the National Toxicology Program (NTP) 2-yr carcinogenicity study. This current amended report on Pyrogallol is an updated version of the 2007 document and includes the studies considered in the 2007 document, as well as the new studies available since then. Excerpts from the summaries of the 1991 report are disseminated throughout the text of this document, as appropriate, and are identified by *italicized text*.

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; this search was last performed September 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.

Some chemical and toxicological data on Pyrogallol included in this safety assessment were obtained from robust summaries of data submitted to the European Chemicals Agency (ECHA) by companies as part of the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) chemical registration process.[4] These data summaries are available on the ECHA database, and when deemed appropriate, those summary data have been included in this report.

CHEMISTRY

Definition and Structure

Pyrogallol (CAS No. 87-66-1) is the benzenetriol that conforms to the structure in Figure 1.[1]

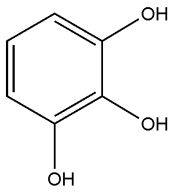


Figure 1. Pyrogallol

Chemical Properties

Pyrogallol is stable in the dark and in the absence of alkali, and sublimes when heated slowly.[2] *It is oxidized easily when in alkaline solutions, and such solution of Pyrogallol are potent reducing agents. A UV spectral analysis of chemically pure Pyrogallol (99%; 0.1% w/v in methanol) showed a single absorbance maximum at 267.5 nm.*

Chemical properties for Pyrogallol are summarized in Table 1. Pyrogallol is a white, odorless crystal with a molecular weight of 126.11.[2] The log P_{ow} (estimated) is 0.97.[5]

Pyrogallol is a potent generator of superoxide anion and other reactive oxygen species (ROS).[6] It also generates a hydroxyl radical by the Haber-Weiss reaction.

Method of Manufacture

Pyrogallol is prepared via the chlorination of cyclohexanol to tetrachlorocyclohexanone, followed by hydrolysis.[2]

Impurities

Technical synthetic-grade Pyrogallol is 90 - 96% pure and technical natural-grade Pyrogallol is not less than 98% pure. Iron (0.001%) and heavy metals (5 ppm max.) are impurities that have been detected in Pyrogallol.[2]

As part of the specifications for use as a dye in catgut sutures used in surgery, Pyrogallol must not have more than 20 ppm lead or 3 ppm arsenic (21 CFR 73.1375).

USE

Cosmetic

The safety of the cosmetic ingredient 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 Pyrogallol 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.[7] 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, Pyrogallol is reported to be used in 20 formulations, and the product categories with reported use were false eyelashes, eyelash and eyebrow adhesives, other eye makeup preparations, eyelash and eyebrow dyes, and nail polish and enamels (Table 2); use in hair dyes and colors is not reported.[8,9] The concentration of use survey using MoCRA product categories conducted by the Council in 2025 found no uses for Pyrogallol, but manufacturers indicated that Pyrogallol is a component of some plant extracts and may be found in cosmetics in low concentrations as an incidental ingredient.[10] As a point of reference, in 1989, the maximum concentration of use range was reported to be < 0.1 - 5% in hair dyes and colors.[2]

This ingredient is considered a coal tar hair dye for which regulations require caution statements and instructions regarding patch tests in order to be exempt from certain adulteration and color additive provisions of the US Federal Food, Drug, and Cosmetic Act (FD&C Act). In order to be exempt, the following caution statement must be displayed on all coal tar hair dye products:

> Caution - this product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.

Product labels shall also bear patch test instructions for determining whether the product causes skin irritation. However, whether or not patch testing prior to use is appropriate is not universally agreed upon. The Panel recommends that an open patch test be applied and evaluated by the beautician and/or consumer for sensitization 48 h after application of the test material and prior to the use of a hair dye formulation. Conversely, a report in Europe suggests that self-testing has severe limitations, and may even cause morbidity in consumers.[12,13] Hair dye products marketed and sold in the US, though, must follow the labeling requirements established by the FD&C Act.

However, according to the RLD, Pyrogallol has been reported to be used in eye makeup preparations, eyelash and eyebrow dyes, and nail polish and enamels. Pyrogallol is exempt from certain adulteration and color additive provisions of the FD&C Act ***only*** when used as coal tar hair dye ingredients. With regard to the reported use in eye makeup preparations and manicuring preparations, the FD&C Act mandates that color additives must be approved by FDA for their intended use before they are used. Pyrogallol is not approved color additives in non-hair dye cosmetic products, and thereby, use in eye makeup products and manicuring preparations is not permitted. Furthermore, as stated above, the FD&C Act also specifies that coal tar hair dyes must not be used for dyeing the eyelashes or eyebrows.

It is possible that some products containing Pyrogallol 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 this ingredient as listed in the RLD include a designation indicating airbrush application, so it is possible that this ingredient is used with airbrush delivery systems, but not reported as such. Additionally, 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 this ingredient was to be used in airbrush formulations, the data are insufficient to evaluate the exposure resulting from cosmetics applied in such a manner.

Under European regulations for cosmetic products, Pyrogallol is listed in Annex II, the list of substances prohibited in cosmetic products in Europe.[14]

Non-Cosmetic Uses

Non-cosmetic uses of Pyrogallol include developer in photography; making colloidal solutions of metals; in leather, wool, and fur dyeing; and process engraving.[2] *It is also reported to be used in manufacturing other dyes; in manufacturing pesticides; as a reagent for antimony and bismuth in analytical chemistry; and as an active reducer for gold, silver, and mercury salts.*

Pyrogallol is exempt from certification as a color additive in drugs when used in combination with ferric ammonium citrate for coloring plain and chromic catgut sutures for use in general and ophthalmic surgery (21 CFR 73.1375).

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

The percutaneous absorption of Pyrogallol was determined using 6 minipig skin samples (500 µm thick) in Franz diffusion cells.[15] Pyrogallol (4%) and 6% hydrogen peroxide were mixed 1:1 to yield 2% Pyrogallol, which was applied to the pig skin at 10 µl per 1 cm^2. After 30 min, the skin was wiped with an alcohol swab and then again after 24 h. The stratum corneum was collected using tape stripping (15 times) and the skin was then cut into 8 pieces. Skin swabs at 30 min and 24 h, the stratum corneum, and skin samples used in each step were put into 10 ml of water, sonicated for 1 h, and refrigerated for 24 h prior to analysis. Receptor fluid (phosphate buffered saline) was collected at 0, 1, 2, 4, 8, 12, and 24 h and refrigerated prior to analysis. Analysis was performed by high-performance liquid chromatography (HPLC). The recovery of Pyrogallol was 48.4 ± 7.6% for 30 min swab samples and 3.9 ± 0.8% for 24 h swab samples. Pyrogallol recovery was 2.3 ± 0.7% from the stratum corneum samples, 10.7 ± 4.7% from skin samples, and 15.3 ± 1.6% from receptor fluid samples. The total recovery was 80.5 ± 6.8% and the total absorption was 26.0 ± 3.9% (91.9 ± 13.7 µg/cm^2).

Absorption, Distribution, Metabolism, and Excretion

In Vitro

In an investigation of oxidoreductive (redox) reactions in human erythrocytes, Pyrogallol (100 mM) oxidized human oxyhemoglobin to methemoglobin and reduced human methemoglobin to oxyhemoglobin.[16] Since superoxide dismutase (SOD) and catalase inhibited these reactions extensively, active oxygen species, such as superoxide and hydrogen peroxide, were considered to be involved in the redox reaction of human hemoglobin by Pyrogallol. It was also found that the metabolism of Pyrogallol to purpurogallin occurred quickly in human erythrocytes, i.e., when Pyrogallol was added to human erythrocyte suspensions, it oxidized intracellular hemoglobin and produced purpurogallin. The metabolism of Pyrogallol to purpurogallin was explained by the Pyrogallol oxidation with the superoxide and hydrogen peroxide that was produced during the redox reactions of human hemoglobin with Pyrogallol.

Animal

Following administration to albino rats via gavage or intraperitoneal injection, Pyrogallol (100 mg/kg) was not found in urine samples that were not subjected to acid hydrolysis.[2] *However, thin-layer chromatography detected Pyrogallol, 2-O-methylpyrogallol, and resorcinol in hydrolyzed urine samples. Resorcinol was also detected in rat fecal samples that had been incubated with Pyrogallol, indicating that Pyrogallol could have been metabolized to resorcinol. Following the intraperitoneal injection of Pyrogallol (60 mg/kg) into female inbred strain mice, the maximum concentration in the brain (28.4 µg/wet weight) was found at 10 min. At 15 min post-injection, the concentration of Pyrogallol approached zero.*

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

An LD_{50} could not be determined in an acute dermal study of Pyrogallol (92.2% or 98.8% pure) in rats.[2] *The test material was applied for 24 h via occlusive patches on the backs of 6 males and 6 females at a concentration of 500 mg/ml in distilled water. No further details on the results were provided.*

In an acute dermal toxicity study performed in accordance with Organisation for Economic Co-operation and Development (OECD) test guideline (TG 402), 3 female Wistar rats received 2000 mg/kg Pyrogallol in 0.4 ml ultra-pure water on clipped skin.[4] The test material was applied under a semi-occlusive patch for 24 h. At the end of the contact period, the patch was removed, and the test site was washed and dried. No mortalities, skin reactions, or clinical signs of toxicity were observed at up to 14 d post-treatment. No abnormalities were observed at necropsy. The LD_{50} for Pyrogallol in this study was greater than 2000 mg/kg.

Oral

The oral LD_{50} values for male and female Sprague-Dawley rats dosed with 283 to 1600 mg/kg Pyrogallol (92.2% pure) in distilled water were 1270 and 800 mg/kg, respectively. The oral LD_{50} values for male and female Sprague-Dawley rats dosed with 566 to 2261 mg/kg Pyrogallol (98.8% pure) in distilled water were 1270 mg/kg and 848 mg/kg, respectively. In another study, the oral LD_{50} of a 50% solution of Pyrogallol in dimethyl sulfoxide (DMSO) was 1800 mg/kg in male Sprague-Dawley rats.

Short-Term Toxicity Studies

Oral

The oral toxicity of Pyrogallol was evaluated using 5 deer mice.[2] Twenty-five wheat seeds, treated with 2% (w/w) Pyrogallol, were placed in the cage of each mouse daily for 3 d. The number of wheat seeds consumed daily was recorded, and the total number of treated seeds consumed by all mice during the 3-d period was subtracted from the total number of seeds available. The difference was converted into what was termed the feed reduction, defined as the percentage of seeds refused. The average amount of Pyrogallol (mg/kg/d) ingested without inducing > 50% mortality was 1240 mg/kg/d.

Subchronic Toxicity Studies

Dermal

A hair dye formulation containing 0.4% Pyrogallol was mixed with an equal volume of 6% hydrogen peroxide prior to dermal application to 6 male and 6 female New Zealand White rabbits 2 times/wk for 13 wk.[2] Slight thickening of the skin was observed at the sites where the dye was applied. Statistically significant differences in clinical chemistry and hematological values were observed between the treatment and control groups (lower alkaline phosphatase values in females and males ($p < 0.05$) and higher hemoglobin in females ($p < 0.05$)). No adverse effects were observed in urinalyses or in gross or microscopic examinations.

In a 3-mo study performed by the NTP, groups of 10 male and 10 female B6C3F1/N mice received dermal applications of Pyrogallol in 95% ethanol.[17] Doses for the mice were 0, 38, 75, 150, 300, or 600 mg/kg at a dose volume of 2.0 ml/kg. At 4 wk and at study end, serologic analyses were performed on 5 male and 5 female sentinel mice, each. The animals received the test material 5 d/wk for 14 wk. The test material was administered over the application site, which extended from the mid-back to the interscapular area; the site was clipped 24 h before the first dose and weekly thereafter. Clinical findings were recorded initially, weekly, and at the end of the studies. Blood was collected from mice at study termination for hematology. At the end of the studies, samples were collected for sperm motility and vaginal cytology evaluations in the vehicle control, 150, 300, and 600 mg/kg groups. Necropsies were performed on all core study animals. The heart, right kidney, liver, lung, right testis, thymus, thyroid gland, and uterus were weighed. Complete histopathologic examinations were performed on vehicle control and 600 mg/kg mice.

All mice survived until study end. The final mean body weights and body weight gains of dosed groups of males and females were similar to those of the vehicle controls. Treatment-related clinical findings included brown staining and irritation of the skin at the site of application. There were no changes in the hematology values of mice attributable to the dermal administration of Pyrogallol. No biologically-significant organ weight changes were noted in males or females. There were no significant differences compared to the vehicle controls in sperm parameters of male mice receiving any dose or in the estrous cyclicity of female mice receiving 300 or 600 mg/kg Pyrogallol. The alteration in estrous cyclicity in the 150 mg/kg group was not considered biologically relevant. Microscopic incidences of squamous hyperplasia, hyperkeratosis, and chronic active inflammation of the skin at the site of application were significantly increased in all dosed groups of males and females. These lesions occurred in nearly all of the treated mice, and the severities of these lesions ranged from minimal to mild, and in general, increased with increasing dose. Ulcer (graded as mild) at the application site occurred in one 300 mg/kg male, two 600 mg/kg males, and three 600 mg/kg females. One 600 mg/kg female had minimal epidermal necrosis at the site of application. A significantly increased incidence of hematopoietic cell proliferation of the spleen was observed in 600 mg/kg male mice.

The NTP also performed a 3-mo dermal study of Pyrogallol in 95% ethanol on groups of 10 male and 10 female F344/N rats in the same manner as the mice. Doses were 0, 9.5, 18.75, 37.5, 75, or 150 mg/kg bw at a dose volume of 0.5 ml/kg. Groups of 10 male and 10 female rats were administered the same doses for 23 d for what was deemed a special study. Blood was collected from special study rats on days 4 and 23 and from main study rats at study termination for hematology, clinical chemistry, and thyroid hormone analyses. At the end of the studies, samples were collected for sperm motility and vaginal cytology evaluations on rats in the vehicle control, 37.5, 75, and 150 mg/kg groups. Complete histopathologic examinations were performed on vehicle control and 150 mg/kg rats.

All rats survived until study end except for one vehicle control female. The mean body weight gain of 150 mg/kg females was less than that of the vehicle controls; otherwise, the final mean body weights and body weight gains of dosed groups of males and females were similar to those of the vehicle controls. Treatment-related clinical findings included brown staining and irritation of the skin at the site of application. No changes in the hematology, serum clinical chemistry, or thyroid hormone values from treatment with Pyrogallol were observed. No biologically significant organ weight changes were noted in males or females. No significant differences were observed in sperm parameters of male rats or the estrous cyclicity of female rats administered 37.5, 75, or 150 mg/kg Pyrogallol when compared to the vehicle controls. Microscopic

incidences of squamous hyperplasia, hyperkeratosis, and chronic active inflammation of the skin at the site of application were significantly increased in all dosed groups of males and females. These lesions were observed in nearly all of the treated rats, and the severities of these lesions ranged from minimal to moderate, and in general, increased with increasing dose. One male rat in the 150 mg/kg group had an ulcer of the skin. The stratum corneum layer of the skin at the test site in dosed rats often had a yellow-brown discoloration, which was attributed to absorption of the test material and was most evident at higher doses.[17]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Dermal

The teratogenicity of a hair dye formulation containing 0.4% Pyrogallol was evaluated using 20 Charles River CD female rats.[2] *The hair dye (2 ml/kg) was applied to the shaved dorsoscapular area of each animal on days 1, 4, 7, 10, 13, 16, and 19 of gestation. Three groups of untreated rats (unshaved) served as controls. Animals in the positive control group were given acetylsalicylic acid (250 mg/kg) via gavage on days 6 to 16 of gestation. The dams were killed on day 20 of gestation via chloroform anesthesia, and fetuses were removed via cesarean section. One third of the fetuses from each litter were examined for visceral anomalies. The remaining fetuses were examined for skeletal anomalies. Toxic effects were not observed in experimental or control dams throughout the study. The mean numbers of corpora lutea, implantation sites, and live fetuses in experimental groups were not significantly different from those in control groups. There were also no significant differences in the number of females with resorption sites and the mean number of resorptions per pregnancy. The incidence of fetal soft tissue and skeletal anomalies in experimental groups was not significantly different from that of negative control groups. A significant increase in the number of fetuses with skeletal and soft tissue anomalies and in the number of dead or resorbed fetuses was observed in the positive control group.*

A multigeneration reproduction study was conducted using Charles River CD rats.[2] *A total of 40 males and 40 females were tested with a hair dye formulation that contained 0.4% Pyrogallol. The dye was mixed with an equal volume of 6% hydrogen peroxide and applied (0.5 ml) to the skin twice per week throughout mating, gestation, and during the period of lactation to weaning of the F_{1b}, F_{2b}, and F_{3c} litters of the respective generations. There were no treatment-related changes in general behavior and appearance, body weight, or survival in parents or offspring. However, mild skin reactions, in treated animals, were noted intermittently throughout the study. Fertility, gestation, and viability indices were comparable between control and experimental groups. Additionally, there were no treatment-related gross or microscopic lesions observed in F_{1b} parental rats or F_{3b} weaning rats.*

Oral

No significant teratogenic effects were observed in the offspring of female Sprague-Dawley rats dosed via gavage with 100, 200, or 300 mg/kg Pyrogallol in propylene glycol on days 6 - 15 of gestation.[2] *A significant decrease in mean maternal weight gains occurred in rats on gestation days 6 - 16 in the 300 mg/kg dose group. This dose group also had smaller fetuses and a significant increase in the total number of resorptions.*

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/sites/default/files/Genotoxicity_ResourceDocument_062026.pdf for the identification of such study types.) Although these assays may be reported in the published literature, unpublished reports, or data submissions, the results from these assays (as identified in the guidance) are of limited interpretability and therefore, the studies are not summarized herein.[2]

In several Ames tests, Pyrogallol (up to 5000 µg/plate) was mutagenic to Salmonella strains TA98, TA100, and/or TA1537.[2] *Technical synthetic Pyrogallol (up to 80 µg/ml; in distilled water) was mutagenic to L5178Y mouse lymphoma cells, with and without metabolic activation. Technical synthetic Pyrogallol (up to 1000 µg/ml; in distilled water) also induced chromosomal aberrations in human lymphocytes, with and without metabolic activation. Pyrogallol (at 0.1 mg/ml) induced chromatid breaks and exchanges in cultures of Chinese hamster ovary (CHO) cells, with and without metabolic activation. In an in vivo micronucleus test, Pyrogallol (252 mg/kg; administered intraperitoneally) significantly increased the percentage of micronucleated polychromatic erythrocytes in mouse bone marrow smears over that of controls. Pyrogallol (up to 0.03 M solution; administered intraperitoneally) also induced chromatid breaks in mouse bone marrow cells.*

In vitro and in vivo genotoxicity studies on Pyrogallol summarized here are detailed in Table 3. In the in vitro studies, Pyrogallol (at up to 1000 µg/plate) caused gene mutations in several Ames tests; however, results in Ames tests were negative for 3 hair gel formulations containing up to 1.5% Pyrogallol (tested at up to 5000 µg/plate).[3,17-21] In a chromosomal aberration test, Pyrogallol was clastogenic in a pH-dependent manner; e.g., at pH 6.0, a significant increase in chromosomal aberrations was observed at 60 and 80 µM, and at pH 7.4 and 8.0, significant chromosomal aberrations were induced at < 80 µM.[22] In studies examining DNA damage, Pyrogallol (up to 30 µg/ml) produced an approximately 30-fold increase in p53-responsive luciferase activity, with the maximal response occurring at 15 µg/ml.[23] DNA double-strand breaks were observed

in a neutral comet assay in p53R cells exposed to Pyrogallol at 15 µg/ml. In vivo, Pyrogallol was not genotoxic in mouse micronucleus tests when tested at up to 600 mg/kg in ethanol (administered dermally) or saline vehicles (administered intraperitoneally), and results with 3 hair gel formulations containing up to 1.5% Pyrogallol (administered orally; 2000 mg/kg bw) were also negative.[17,20]

CARCINOGENICITY STUDIES

Dermal

In a dermal carcinogenicity study, groups of 50 female Swiss mice received 5, 25, or 50% Pyrogallol in acetone on shaved dorsal skin twice/wk for 120 wk.[2] *In all treatment groups, the number of neoplasms in mice treated dermally with Pyrogallol in acetone was not significantly different from that of controls, and no skin neoplasms were observed. A similar study performed in groups of 5 New Zealand rabbits using the same test concentrations in acetone or methanol for 160 wk also was not carcinogenic. The dermal carcinogenicity of an oxidative hair dye formulation containing 0.49% Pyrogallol and 6% hydrogen peroxide in aqueous solution was evaluated in groups of 60 male and 60 female mice (strain not reported). The mice received the test material once/wk for 20 mo. No significant differences in the occurrence of hepatic hemangiomas, pulmonary adenomas, or malignant lymphomas were observed between the treated group and the controls. In a subcutaneous study, histiocytomas were noted at the exposure sites 3 out of 9 male and 1 out of 10 female Fischer rats that received Pyrogallol (details on concentration not available) in 50% DMSO. No neoplasms were observed in the control animals that received only DMSO.*

In the 2-yr studies performed by the NTP, groups of 50 male and 50 female B6C3F1/N mice and F344/N rats received dermal applications of Pyrogallol in 95% ethanol.[17] Doses for both species were 0, 5, 20, or 75 mg/kg, and dosing occurred 5 d/wk for up to 104 (rats) or 105 (mice) wk. The dose volumes were 2.0 ml/kg for mice and 0.5 ml/kg for rats. Prior to the start of the study, 5 male and 5 female mice and rats were randomly selected for parasite evaluation and gross observation for evidence of disease. All animals were observed twice daily. Clinical findings were recorded monthly beginning at week 5. Body weights were recorded initially, weekly for 13 wk, monthly thereafter, and at study end. Complete necropsies and microscopic examinations were performed on all mice and rats. At necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were examined microscopically.

The survival of treated male mice was similar to that of the vehicle control group. The survival of 75 mg/kg female mice was significantly decreased; 23 of the 29 deaths were due to lesions diagnosed grossly as ulcers at the site of application. The mean body weights of 75 mg/kg female mice were generally > 10% less than those of the vehicle controls during year 2 of the study; otherwise, the mean body weights of dosed groups of male and female mice were similar to those of the vehicle control groups throughout the study. Irritation and/or ulceration of the skin at the test sites were the only treatment-related clinical findings, which were observed mostly in the 20 and 75 mg/kg male and female groups. In the 75 mg/kg females, the incidence of squamous cell carcinoma in the skin at the site of application was significantly greater than that in the vehicle control group. Two 75 mg/kg males had squamous cell papillomas. The incidences of hyperplasia and hyperkeratosis were significantly increased in all male and female dose groups. The incidences of inflammation, fibrosis, and pigmentation at the site of application were significantly increased in the 20 or 75 mg/kg male and female mice. The incidences of sebaceous gland hyperplasia and ulcer were significantly increased in the 75 mg/kg male and female mice. The non-neoplastic lesions at the site of application appeared to be more severe in female mice. Although skin lesions were consistently found at the test site, a few treated mice also had morphologically similar lesions in the skin of the neck and back immediately adjacent to the site of application. These lesions were considered related to the test material spreading to or beyond the margins of the clipped skin after application. One 75 mg/kg female had a squamous cell carcinoma of the skin of the right forelimb. The incidences of bone marrow hyperplasia were significantly increased in male mice administered 5 mg/kg and male and female mice administered 75 mg/kg. In female mice exposed to 75 mg/kg, the incidences of lymphoid hyperplasia of the axillary, inguinal, and mandibular lymph nodes, as well as incidence of hyperplasia of the mammary gland, were significantly increased compared to those in the controls. Additionally, the incidence of hematopoietic cell proliferation of the adrenal cortex in 75 mg/kg female mice was significantly increased compared to those in the control group.[17]

Survival of the treated male and female rats was similar to that of the controls. Mean body weights of the treated male and female rats were also similar to the that those of the controls throughout the 2 yr. Irritation of the skin at the site of application was the only treatment-related clinical finding, which was observed in the 20 and 75 mg/kg male and female groups. The incidences of hyperplasia and hyperkeratosis (except hyperkeratosis in 5 mg/kg males) in all treated groups of male and female rats were significantly greater than seen in the controls. The incidences of inflammation were significantly increased in 75 mg/kg males and 20 and 75 mg/kg females. The incidences of sebaceous gland hyperplasia were significantly increased in male and female rats administered 20 or 75 mg/kg. In male rats, the incidence of squamous cell papilloma in the 75 mg/kg group was increased but was not significantly different from that in the control group. However, the incidence of squamous cell papilloma in 75 mg/kg males exceeded the historical control ranges for ethanol dermal studies and for all routes. In the 75 mg/kg males, single squamous cell papillomas occurred on the ear of 1 rat and on the dorsal surface of the nose of 2 rats, but because these lesions did not occur at the site of application, they were not considered to be treatment-related. Increased incidences of malignant mesothelioma in 5 and 75 mg/kg male rats were not statistically

significant, and increased incidences of mononuclear cell leukemia in 20 and 75 mg/kg female rats, while statistically significant when compared to the vehicle controls, were still within the historical control ranges.[17]

At the end of these 2-yr dermal studies, the NTP concluded that there was equivocal evidence of carcinogenic activity of Pyrogallol in male B6C3F1/N mice based on the increased incidences of squamous cell papilloma of the skin at the treatment site. Additionally, there was some evidence of carcinogenic activity of Pyrogallol in female B6C3F1/N mice, also based on the increased incidences of squamous cell papillomas at the treatment site. In F344/N rats, there was no evidence of carcinogenic activity of Pyrogallol in males or females.[17]

An analysis of the above NTP study found that while the survival of treated rats and male mice was comparable to the controls, survival of the female mice that received 75 mg/kg Pyrogallol was significantly decreased compared to controls.[24] Additionally, incidences of microscopic non-neoplastic lesions at the treatment site were significantly higher in all dosed groups of mice and rats in both the 3-mo and 2-yr dermal studies. The hyperplasia, hyperkeratosis, and inflammation observed in the 2-yr study was observed to be more severe in mice than in rats, and in the mice, it tended to be more severe in females than in males. The incidences of squamous cell carcinoma and squamous cell papillomas at the test site in the 75 mg/kg female mice and the 75 mg/kg male mice, respectively, were greater than controls. This analysis concluded that Pyrogallol was carcinogenic in female mice and may have caused tumors in male mice.

Hyperplasia

Pyrogallol (1% in the diet) was fed by continuous oral administration to groups of 15 male Syrian golden hamsters for 20 wk.[25] The control group (15 hamsters) was fed basal diet. Mild hyperplasia of the forestomach was noted in 15 hamsters ($p < 0.001$, compared to control group). Four hamsters had moderate hyperplasia of the forestomach. Oral dosing induced neither severe hyperplasia nor papillomas. Seven hamsters fed basal diet only had mild hyperplasia of the forestomach, and 1 hamster fed basal diet only had moderate hyperplasia of the forestomach.

Tumor Promotion

Pyrogallol (0.25 to 3.0 µg/ml) was used to assess the usefulness of the Chinese hamster V79 cell metabolic cooperation assay to predict the tumor-promoting activity of selected chemicals.[26] Results were positive for Pyrogallol at one laboratory and negative at the other. Chemicals were scored as positive (at least two concentration levels statistically different from the control), equivocal (only one concentration statistically different), or negative. Overall, the results for Pyrogallol were classified as equivocal.

Co-Carcinogenicity

Dermal

In a group of 50 female ICR/HA Swiss mice, Pyrogallol (5 mg in acetone) was reported to be an active co-carcinogen when applied to clipped dorsal skin with benzo(α)pyrene (5 µg/0.1 ml acetone).[2] Additional groups of 50 mice received either benzo(α)pyrene or Pyrogallol alone. Applications were made 3 times/wk for 440 d. Ten of 50 treatment mice that received benzo(α)pyrene alone developed squamous carcinomas, whereas 33 of the 50 mice treated with Pyrogallol and benzo(α)pyrene developed squamous carcinomas of the skin. Neoplasms were not observed in the mice that received Pyrogallol alone.

Anti-Cancer Activity

The antiproliferative activity of Pyrogallol was studied using human tumor cell lines.[27] The effects of this chemical on in vitro cell growth were presented; the inhibition of tumor cell proliferation was consistently observed. The IC_{50} of Pyrogallol on K562, Jurkat, HEL, and Raji cell lines was found to be in the range of 10 to 30 µM.

Pyrogallol was tested at concentrations of 30, 60, and 90 µg/ml in two non-small cell lung cancer (NSCLC) cell lines (A549 and H460).[28] Concentration-related increases in G2/M-phase cell-cycle arrest and apoptosis were reported. At 90 µg/ml, Pyrogallol significantly increased the proportion of cells arrested in the G2/M phase after 24 h and the proportion of apoptotic cells after 48 h, compared with the respective controls. The induction was due to the up-regulation of p21 in a p53-dependent manner. A blockade of p53 and p21 effectively abolished the cell cycle arrest at the G2/M phase. Meanwhile, p53 inhibition has been found to abrogate the Pyrogallol-induced apoptosis of the two NSCLC cells. In vivo mouse experiments demonstrated that Pyrogallol (20 mg/kg/d by intragastric administration) exerted growth inhibition on NSCLC with low toxicity through the same molecular mechanism as observed in vitro.

The anticancer properties of Pyrogallol (0 - 20 µg/ml) were investigated using ovarian carcinoma cell line A2780.[29] Following treatment for 48 h, Pyrogallol significantly decreased cell viability in a concentration-dependent manner at concentrations of 3 - 20 µg/ml; the half-maximal inhibitory concentration (IC_{50}) was 5.32 µg/ml. Combined treatment with Pyrogallol and cisplatin produced greater reductions in cell viability than either agent alone. The combination treatment increased the induction of apoptosis by up to 2.5-fold compared to single treatments. Quantitative real-time polymerase chain reaction (qPCR) analysis showed significant increased miR-15a expression and decreased expression of its target genes, CDC25A and KRAS, following treatment with Pyrogallol and/or cisplatin.

In Hep3B and Huh7 hepatocellular carcinoma cells, Pyrogallol (5 - 80 µM) significantly decreased cell viability in a concentration-dependent manner following treatment for 24 h.[30] Pyrogallol (20 - 80 µM) also reduced colony formation and

increased the proportion of cells in the S-phase, decreased the protein expression of cyclinD1, cyclin E, cyclin A, c-Myc, S-phase kinase-associated protein 2 (Skp2), p-AKT, and PI3K, and increased the protein expression of p27. At 80 µM, Pyrogallol reduced the fluorescent expression of cyclin E in both cell lines and disturbed the interactions between Skp2, p27, and c-Myc in Huh7 cells. Pyrogallol (80 µM) also increased miR-134 expression in Huh7 cells, while inhibition of miR-134 partially reversed the Pyrogallol-induced decreases in c-Myc, cyclin E and cyclin D1 expression.

The anti-tumor effects of Pyrogallol were investigated in C57BL/6 mice with xenograft tumors.[31] The tumor-bearing mice were treated with 40 mg/kg bw Pyrogallol intravenously for 21 d. Phosphate buffered saline was the vehicle control and doxorubicin was the positive control. Tumor size was significantly reduced (96%) in a time-dependent manner similar to that of doxorubicin. Tumor-bearing mice treated with Pyrogallol had a mild decline in body weight.

In a study evaluating the cytotoxic and pro-apoptotic effects of Pyrogallol on rat C6 glioma cells, the cells were treated with 20, 40, or 80 µM for up to 72 h.[32] Cell viability, as measured by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, decreased in a dose- and a time-dependent manner, with IC_{50} values of 40 µM at 24 h and 15 µM at 72 h. Intracellular ROS and disrupted mitochondrial membrane potential were also observed. Flow cytometry with fluorescent staining revealed a dose-dependent increase in early and late apoptotic populations with significant G0/G1 phase cycle arrest. Consistently, biochemical assays demonstrated elevated lipid peroxidation and reduced activities of the antioxidant enzymes SOD and catalase. qPCR and enzyme-linked immunosorbent assay (ELISA) analyses found upregulation of pro-apoptotic genes and proteins (Bas and cytochrome c), with downregulation of the anti-apoptotic marker, Bcl-2.

OTHER RELEVANT STUDIES

Gene Expression

The induction of c-*fos* and c-*jun* gene expression by phenolic antioxidants, including Pyrogallol, was studied in quiescent human hepatoma HepG2 cells.[33] Following the treatment of the cells with 200 µM Pyrogallol, the levels of c-f*os* and c-*jun* mRNAs were substantially increased. Phenolic antioxidants specifically induce expression of the c-*fos* and c-*jun* mRNAs. The antioxidant-specific induction of c-f*os*/chloramphenicol acetyltransferase promoter constructs in transient transfections indicates that at least a portion of this response is transcriptional.

Effect on ATPase Activity and Antigen Expression

The effect of Pyrogallol on ATPase activity and Ia antigen expression was studied using murine epidermal Langerhans cells.[34] BALB/c mice (8 mice/group) were smeared with ointments containing different concentrations of Pyrogallol (1, 5, 10, or 20%) and tested 3 d later for ATPase and Ia positive Langerhans cells. A statistically significant reduction of ATPase positive Langerhans cells was observed at Pyrogallol concentrations of 5% or higher ($p < 0.05$).

Endocrine Effects

The antithyroid activity of Pyrogallol was studied by porcine thyroid peroxidase (TPO)-catalyzed iodination of bovine serum albumin.[3] The concentration at which 50% inhibition of porcine thyroid peroxidase activity (ID_{50}) occurred was determined. The mean ID_{50} for Pyrogallol (based on 5 experiments) was 3.8 ± 0.12 nmol/ml). The known TPO inhibitor and antithyroid drug 6-*N*-propyl-2-thiouracil (PTU) served as the reference standard. The mean ID_{50} for PTU was 7.2 ± 0.16 nmol/ml.

Cytotoxicity

No evidence of plasma membrane damage was observed in human diploid embryonic lung fibroblasts (cell line MRC-5) following treatment with a 25 mM solution of Pyrogallol for 30 min.[2] *In another study, ciliostasis was noted in tracheal organ cultures prepared from chicken embryos within 15 min of exposure to 5mM Pyrogallol in DMSO.*

The role of superoxide anion in neuronal cell injury induced by ROS was studied in PC12 cells using Pyrogallol as a donor to release the anion.[35] Cell death was assessed by the measurement of released lactate dehydrogenase (LDH) into the culture medium. Pyrogallol at concentrations greater than 0.2 mM caused a time-dependent cell death. After exposure to 0.5 mM Pyrogallol, the released LDH rapidly increased up to approximately 72% at 5 h. Mild cell death was observed at 0.2 mM Pyrogallol, when approximately 56% of the LDH was released at 24 h. However, at 0.1 mM Pyrogallol, the released LDH level was comparable to that of control cells.

Cytotoxicity of Pyrogallol was evaluated using *Escherichia coli* strains that express mammalian catalase gene derived from catalase mutant mice (Cs^b) and wildtype (Cs^a). Pyrogallol was more toxic to Cs^b than to Cs^a ($p < 0.05$), and the viability of the strains decreased as the concentration of Pyrogallol increased (no further details provided). The addition of antioxidants lessened the toxic effects of Pyrogallol on both strains. The researchers concluded that Pyrogallol cytotoxicity may be attributed in part to ROS formation.

Wild type and *wat1/pop3* delete *Schizosaccharomyces pombe* cells were unable to grow on plates containing 0.5 - 1.5 mM Pyrogallol in a dose-dependent manner.[36] The *wat1/pop3* delete cells also exhibited higher sensitivity against Pyrogallol as compared to the wild type cells, which suggested that Pyrogallol induces oxidative stress. The exposure of Pyrogallol (2 mM for 3 h) also led to the production of ROS (Pyrogallol tested at 2 mM) and affected the sporulation of *S. pombe* (Pyrogallol tested at 0.5 - 2 mM).

Pyrogallol (20 - 100 µg/ml) protected HeLa cells from *Vibrio vulnificus*-induced cytotoxicity.[37] Pyrogallol also decreased the growth of *V. vulnificus*; this inhibitory effect was more significant during the log phase than the stationary phase. No growth was observed for the *katG*- mutant in the presence of Pyrogallol (50 µg/ml) even after 24 h, whereas the wild-type strain demonstrated growth recovery following a prolonged lag phase. Pyrogallol-mediated growth inhibition of the *katG*- mutant strain was partially rescued by exogenous catalase treatment. These results indicated that the mechanism by which Pyrogallol inhibits the growth and cytotoxicity of *V. vulnificus* likely involves polyphenol-induced prooxidant damage.

Pyrogallol (50 µM in hydrogen peroxide) inhibited growth of As4.1 juxtaglomerular cells.[38] It also induced apoptosis and the loss of mitochondrial membrane potential and increased the level of p53 protein. Intracellular superoxide anion level was increased in Pyrogallol-treated cells. These effects were attenuated by mitogen-activated protein kinase inhibitors.

The cytotoxic effects of Pyrogallol were studied using rat C6 glioma cells in an MTT assay.[32] The cells were treated with 10, 20, 40, 80, or 100 µM Pyrogallol for 24, 48, or 72 h. A significant dose- and time-dependent effect on cell viability was observed. IC_{50} values decreased from 40 µM at 24 h to 15 µM at 72 h.

Antioxidant Effects

In an oxidative stress study using *Saccharomyces cerevisiae,* the acquisition of oxidative stress resistance in cells pretreated with Pyrogallol (300 µM) was not associated with an induction of endogenous antioxidant defenses as assessed by the analysis of SOD and catalase activities.[39] Pyrogallol increased hydrogen peroxide resistance associated with a reduction in intracellular oxidation and protein carbonylation.

Immunotoxicity

In an immunosuppression study, the addition of Pyrogallol (5 µg/culture) resulted in ≥ 90% suppression of plaque formation and 50% reduction in viability in B lymphocyte cultures from dissociated mouse splenic cell that were incubated with sheep red blood cells for 5 d.

Hepatotoxicity

In a series of studies, male Swiss albino mice were administered Pyrogallol (40 mg/kg/d) intraperitoneally for up to 4 wk..[40-42] Pyrogallol increased alanine aminotransaminase and aspartate aminotransaminase activities, bilirubin levels, hepatic lipid peroxidation, and the expression and catalytic activity of cytochrome P450 2E1 (CYP2E1) and cytochrome P450 1A2 (CYP1A2).[41,42] Conversely, Pyrogallol decreased GST-ya and GST-yc expressions, GST, glutathione peroxidase and glutathione reductase activities, and reduced GSH content. CYP1A1 expression and activity were not significantly altered. Histopathology showed hepatocellular membrane disintegration, cytoplasmic vacuolation and rarefaction, with occasional necrosis and inflammation. Pretreatment with resveratrol or silymarin attenuated many of these effects. In a 4-wk transcriptional-profiling study, Pyrogallol altered the expression of 183 hepatic transcripts (150 up-regulated and 33 down-regulated) associated with oxidative stress, cell cycle, cytoskeletal network, cell–cell adhesion, extra-cellular matrix, inflammation, apoptosis, cell-signaling and intermediary metabolism.[40] These results suggested that Pyrogallol induces multiple molecular events leading to hepatotoxicity.

The hepatotoxicity of Pyrogallol was studied using groups of 4 male and 4 female Wistar albino rats.[43] Pyrogallol was injected intraperitoneally at a dose of 100 mg/kg. At 1 h after dosing, blood was drawn by cardiac puncture for the estimation of serum markers (aspartate aminotransaminase [AST], alanine aminotransaminase [ALT], and alkaline phosphatase). The rats were later killed and livers were removed and processed for malondialdehyde (MDA) and glutathione (GSH) and tissue histology. Pyrogallol produced significant liver damage, as indicated by a marked increase in serum AST and ALT, compared to the control group ($p < 0.05$). The serum AST and ALT increased to 357.0 ± 30.7 IU/I and 147.8 ± 28.4 IU/I, respectively, compared to 208.4 ± 4.1 IU/I and 84.5 ± 19.5 IU/I, respectively, in control animals. However, there was an insignificant change in the levels of alkaline phosphatase in the Pyrogallol-treated group; values for Pyrogallol-treated animals and the control group were 216.6 ± 44.1 IU/I and 240 ± 16.3 IU/I, respectively. Pyrogallol produced significant oxidative stress in liver tissue, as indicated by the marked increase in MDA and GSH levels (markers of oxidative stress), compared to the control group. The MDA levels increased significantly to 311 ± 18.29 nmol/g wet tissue, compared to 170 ± 16.8 nmol/g wet tissue, respectively ($p < 0.05$). GSH levels also increased significantly to 37 ± 2.25 µg/g wet tissue, compared to a control value of 24.4 ± 3.6 µg/g wet tissue ($p < 0.05$). The Pyrogallol-treated rats had mild inflammatory changes in the liver. The changes included cellular infiltration of leukocytes and sinusoidal dilation, even as early as 1 h after Pyrogallol administration.

DERMAL IRRITATION AND SENSITIZATION STUDIES

A primary irritation index score of 0.5 was reported when Pyrogallol (neat in powder form) was applied to abraded and intact albino rabbit skin for 24 h under a patch.[2] *In a skin irritation study, 500 mg/ml Pyrogallol (92.2 or 98.8% w/w pure) in distilled water was slightly irritating to the skin of Dunkin Hartley guinea pigs following a 24-h exposure.*

In a guinea pig sensitization test, female Hartley guinea pigs were induced with subcutaneous injections of 0.01, 0.05, or 0.1 M Pyrogallol and challenged with the same concentrations.[2] *Sensitization reactions were observed in animals at all concentrations. In another guinea pig study, the animals were induced intradermally with 1% Pyrogallol in water and*

topically with 25% Pyrogallol in propylene glycol prior to being challenged with a single topical application of 25% Pyrogallol solution. No sensitization was observed in this study.

Dermal irritation and sensitization studies on Pyrogallol summarized here are detailed in Table 4. Pyrogallol was predicted to be corrosive when tested neat in an MTT assay using reconstructed human epidermis.[4] When diluted in MTT solution in a human skin model, Pyrogallol was predicted to be irritating. Pyrogallol induced a positive irritation response at concentrations as low as 0.125% when tested at up to 10% in a irritancy assay in mice.[44] Quantitative structure–activity relationship ((Q)SAR) software predicted Pyrogallol to cause allergic contact dermatitis (no further details provided).[4] In a mouse ear swelling test conducted as a 2-part study, no significant differences were observed in mice induced with up to 5% and challenged with 0.25% Pyrogallol to those in the control groups; however, a significant increase in percent ear swelling was observed in mice induced with 5% and challenged with 0.5% Pyrogallol.[44] In a local lymph node assay (LLNA) conducted as a 3-part study, Pyrogallol induced a significant increase in proliferation of lymph node cells (stimulation index, SI > 3) at concentrations of 0.5% and higher. No reduction of contact sensitization was observed after treatment with 5 - 10% Pyrogallol in ointment in an ear swelling study to determine if the material altered sensitization to1-fluoro-2,4-dinitrobenzene (DNFB). [34]

OCULAR IRRITATION STUDIES

Animal

In a study involving 6 male New Zealand white rabbits, 100 mg Pyrogallol (neat in powder form) induced ocular irritation.[2] *In another 6 male New Zealand white rabbits, Pyrogallol (0.1 ml) was not an ocular irritant when tested at a concentration of 1% in propylene glycol.*

CLINICAL STUDIES

Sensitization reactions were noted in 3 of 25 patients with leg ulcers that were patch tested with Pyrogallol (concentration tested not reported).[2] *Patients tested had lesions for 12 mo or greater.*

Multicenter and Retrospective Studies

In a retrospective study, 8230 patients with allergic contact dermatitis were patch tested with cosmetic ingredients over a period of 15 yr (1968 - 1983).[2] *Positive reactions to Pyrogallol (1% in pet.) were not reported.*

Retrospective studies on patients with contact dermatitis are summarized in Table 5. Sensitization rates to 1% Pyrogallol were as high as 5.4%.[45-48] In a retrospective study of sensitization to resorcinol, the sensitization rate to 1% Pyrogallol was 47% (9 out of 19 patients).[49] A retrospective study in Greece found 100% cross-reactivity to *p*-phenylene-diamine and 90.9% cross-reactivity to *p*-toluenediamine in patients that tested positive to Pyrogallol.[48]

Occupational Studies

Assessments of effects in persons occupationally exposed to Pyrogallol are summarized in Table 6. Positive responses ranged from 0 (out of 54 hairdressers tested) to a sensitization rate of 1.3% (out of 302 hairdressers tested).[50-52]

HAIR DYE EPIDEMIOLOGY

Hair dyes may be broadly grouped into oxidative (permanent) and direct (temporary or semi-permanent) dyes. The oxidative dyes consist of precursors mixed with developers to produce color, while direct hair dyes consist of preformed colors. Pyrogallol is reported to be used in oxidative hair dye formulations. While the safety of individual hair dye ingredients is not addressed in epidemiology studies that seek to determine links, if any, between hair dye use and disease, such studies do provide broad information. The Panel determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer. A detailed summary of the available hair dye epidemiology data is available at https://www.cir-safety.org/cir-findings.

SUMMARY

Pyrogallol is reported to function as a hair colorant and a fragrance ingredient in cosmetic products. The Panel first reviewed the safety of Pyrogallol in a report published in 1991, with the conclusion that this ingredient was safe in the present practices of use and concentration. A re-review initiated in 2007 was tabled to await the findings of the NTP 2 yr carcinogenicity study. Because it had been at least 15 years since the Panel reviewed this ingredient last and because the 2007 re-review was never completed, in accordance with the CIR Procedures, the Panel determined that the re-review should be resumed, and revised to include all information that has become available since it was initially tabled.

According to RLD obtained from the FDA in 2025, Pyrogallol is reported to be used in 20 formulations, and the product categories with reported use were false eyelashes, eyelash and eyebrow adhesives, other eye makeup preparations, eyelash and eyebrow dyes, and nail polish and enamels; use in hair dyes and colors is not reported. The concentration of use survey conducted by the Council in 2025 found no uses for Pyrogallol, but manufacturers indicated that Pyrogallol is a component of some plant extracts and may be found in cosmetics in low concentrations as an incidental ingredient. As a point of reference, in 1989, the maximum concentration of use range was reported to be < 0.1 - 5% in hair dyes and colors. Under European

regulations for cosmetic products, Pyrogallol is listed in Annex II, the list of substances prohibited in cosmetic products in Europe.

In a percutaneous absorption study, 4% Pyrogallol and 6% hydrogen peroxide were mixed 1:1 to yield 2% Pyrogallol, which was applied to pig skin for 30 min. The total recovery was 80.5 ± 6.8% and the total absorption was 26.0 ± 3.9% (91.9 ± 13.7 µg/cm^2).

In an acute dermal toxicity study in rats that received Pyrogallol in water under semi-occluded patches for 24 h, the LD_{50} was determined to be greater than 2000 mg/kg (the dose tested). A 14-wk range-finding study in rats tested Pyrogallol in 95% ethanol at 0, 9.5, 18.75, 37.5, 75, and 150 mg/kg dermally. Treatment-related epidermal hyperkeratosis, epidermal squamous hyperplasia, and chronic-active inflammation of the dermis were observed in a dose-dependent manner. The NTP performed a 3-mo dermal study of Pyrogallol in mice and rats at doses up to 600 mg/kg and 150 mg/kg, respectively. Microscopic investigation found incidences of squamous hyperplasia, hyperkeratosis, and chronic active inflammation of the skin at the site of application were significantly increased in all groups of male and female mice and rats in a dose-dependent manner. A significantly increased incidence of hematopoietic cell proliferation of the spleen was observed in 600 mg/kg male mice.

In in vitro genotoxicity studies, Pyrogallol (at up to 1000 µg/plate) caused gene mutations in several Ames tests; however, Ames tests were negative with 3 hair gel formulations containing up to 1.5% Pyrogallol (tested at up to 5000 µg/plate). In a chromosomal aberration test, Pyrogallol was clastogenic in a pH-dependent manner; e.g., at pH 6.0, a significant increase in chromosomal aberrations was observed at 60 and 80 µM, and at pH 7.4 and 8.0, significant chromosomal aberrations were induced at < 80 µM. In studies examining DNA damage, Pyrogallol (up to 30 µg/ml) caused a 30-fold increase in DNA strand breaks in p53R cells, with the maximal response occurring at 15 µg/ml. DNA double-strand breaks were observed in a neutral comet assay in p53R cells exposed to Pyrogallol at 15 µg/ml. In vivo, Pyrogallol was not genotoxic in mouse micronucleus tests when tested at up to 600 mg/kg in ethanol (administered dermally) or saline vehicles (administered intraperitoneally), and results with 3 hair gel formulations containing up to 1.5% Pyrogallol (administered orally; 2000 mg/kg bw) were also negative.

In 2-yr dermal carcinogenicity studies performed by the NTP, mice and rats received up to 75 mg/kg Pyrogallol in 95% ethanol. The NTP concluded that there was equivocal evidence of carcinogenic activity of Pyrogallol in male mice based on the increased incidences of squamous cell papilloma of the skin at the treatment site. Additionally, there was some evidence of carcinogenic activity of Pyrogallol in female mice, also based on the increased incidences of squamous cell papillomas at the treatment site. In rats, there was no evidence of carcinogenic activity of Pyrogallol in males or females.

The results of a tumor promotion study of Pyrogallol were equivocal after 0.25 to 3.0 µg/ml were assayed with Chinese hamster V79 cells. In anti-tumor studies, the IC_{50} of Pyrogallol on several human tumor cell lines was found to be in the range of 10 - 30 µM. Pyrogallol (0-90 µM) induced cell cycle arrest at the G2/M phase and apoptosis in two different NSCLC cell lines. Pyrogallol (0 - 20 µg/ml), with and without cisplatin, significantly increased the death of ovarian carcinoma cell line A2780 via apoptosis. Antiproliferative effects of Pyrogallol (5 - 80 µM) in hepatocellular carcinoma cells via miR-134 activation mediated S-phase arrest and inhibition of PI3K/AKT/Skp2/cMyc signaling. In vivo mouse experiments demonstrated that Pyrogallol (20 mg/kg/d by intragastric administration) exerted growth inhibition on NSCLC with low toxicity through the same molecular mechanism as observed in vitro. Tumor-bearing mice treated with 40 mg/kg bw Pyrogallol intravenously for 21 d were observed with significantly reduced tumor size in a time-dependent manner. Apoptotic effects were observed in a dose-dependent manner in rat C6 glioma cells treated with 20-80 µM Pyrogallol.

Several studies found Pyrogallol to be cytotoxic in bacterial, yeast, rat and human cell lines. These effects were attributed, in part, to ROS formation. In an oxidative stress study in yeast, Pyrogallol (300 µM) increased hydrogen peroxide resistance associated with a reduction in intracellular oxidation and protein carbonylation. Hamsters fed Pyrogallol (1% in diet) continuously for 20 wk had mild to moderate hyperplasia of the forestomach, with no severe hyperplasia or papillomas. Hepatotoxic effects observed in studies with mice treated intraperitoneally with 40 mg/kg Pyrogallol for up to 4 wk included increases in lipid peroxidation, mRNA expression, and catalytic activity of CYP2E1 and CYP1A2, and rats that received 100 mg/kg intraperitoneally had marked increases in serum AST and ALT, MDA and GSH levels in the liver, and mild inflammatory changes in the liver as early as 1 h after receiving Pyrogallol.

Pyrogallol was predicted to be corrosive when tested neat in an MTT assay using reconstructed human epidermis. When diluted in MTT solution in a human skin model, Pyrogallol was predicted to be irritating. Pyrogallol induced a positive irritation response at concentrations as low as 0.125% when tested at up to 10% in a irritancy assay in mice. (Q)SAR software predicted Pyrogallol to cause allergic contact dermatitis. In a mouse ear swelling test conducted as a 2-part study, no significant differences were observed in mice induced with up to 5% and challenged with 0.25% Pyrogallol to those in the control groups; however, a significant increase in percent ear swelling was observed in mice induced with 5% and challenged with 0.5% Pyrogallol. In an LLNA conducted as a 3-part study, Pyrogallol induced a significant increase in proliferation of lymph node cells (SI > 3) at concentrations of 0.5% and higher. No reduction of contact sensitization was observed after treatment with 5 - 10% Pyrogallol in ointment in an ear swelling study to determine if the material altered sensitization to DNFB.

In retrospective studies, sensitization rates to 1% Pyrogallol were as high as 5.4%. In a retrospective study of sensitization to resorcinol, the sensitization rate to 1% Pyrogallol was 47% (9 out of 19 patients). A retrospective study in Greece found 100% cross-reactivity to *p*-phenylenediamine and 90.9% cross-reactivity to *p*-toluenediamine in patients that tested positive to Pyrogallol. Positive responses ranged from 0 (out of 54 hairdressers tested) to a sensitization rate of 1.3% (out of 302 hairdressers tested) in occupational studies.

The Panel determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer.

DISCUSSION

In accordance with its Procedures, the Panel re-evaluates the conclusions of previously-issued reports approximately every 15 years. In 1991, the Panel published a final report on Pyrogallol and concluded that this ingredient was safe for use as a cosmetic ingredient. A re-review was initiated in 2007, which was subsequently tabled to await the findings of the NTP 2 yr carcinogenicity study; this current amended report on Pyrogallol is a continuation of the 2007 document. The Panel noted a lack of relevant safety data, especially data that pertain to new product category uses outside of hair dyes, and determined that the data needs from the Insufficient Data Announcement issued following the June 2025 Panel meeting remain unmet. In order to come to a conclusion of safety for this ingredient, the following additional data are needed:

- Maximum concentration of use in hair dye formulations
- Genotoxicity studies, with metabolic activation, that test for the formation of DNA adducts

The Panel noted the carcinogenic activity observed in mice in both the NTP study and a co-carcinogenicity study, as well as the positive findings in Ames tests and other in vitro genotoxicity studies conducted with and without metabolic activation. Although tumor formation at the site of dermal application was likely driven primarily by chronic irritation and subsequent inflammatory and regenerative processes given the absence of systemic carcinogenic effects, the confinement of tumors to the site of application, and the increased incidence of non-neoplastic inflammatory and proliferative skin lesions, the possibility of a genotoxic mode of action could not be excluded. The in vivo genotoxicity results (e.g., micronucleus assay) were negative; however, without additional data demonstrating whether Pyrogallol can or cannot react with DNA (e.g., through in vitro evaluation of DNA adduct formation), concerns regarding the mode of action underlying the carcinogenic findings could not be fully alleviated.

Pyrogallol has been reported to be used in false eyelashes, eyelash and eyebrow adhesives, and nail polish and enamels. However, this ingredient is exempt from certain adulteration and color additive provisions of the FD&C Act ***only*** when used as a coal tar hair dye ingredient. Accordingly, because Pyrogallol is not an approved color additive in cosmetics products, use in eye makeup products and manicuring preparations is not permitted in the U.S. Furthermore, the Panel noted that the RLD reported uses in eyelash and eyebrow dyes, and reiterated that hair dyes, such as those containing Pyrogallol, should not be applied to the eyebrows and eyelashes in that such use can result in lost or permanently damaged vision.

Additionally, the Panel recognizes that hair dyes containing this ingredient, as coal tar hair dye products, are exempt from certain adulteration and color additive provisions of the Federal FD&C Act when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Panel expects that following this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures. The Panel considered concerns that such self-testing might induce sensitization, but agreed that there was not a sufficient basis for changing this advice to consumers at this time.

The Panel noted heavy metals that may be present in this ingredient. They stressed that the cosmetics industry should continue to use the necessary procedures to minimize impurities in cosmetic formulations according to limits set by the US FDA and Environmental Protection Agency (EPA).

In considering hair dye epidemiology data, the Panel concluded that the available epidemiology studies are insufficient to scientifically support a causal relationship between hair dye use and cancer or other toxicological endpoints, based on lack of strength of the associations and inconsistency of findings. Use of direct hair dyes, while not the focus in all investigations, appears to have little evidence of any association with adverse events as reported in epidemiology studies. However, use of the ingredients in this report as direct hair dyes is not reported.

The Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings) 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 this ingredient is 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 available data are insufficient to make a determination of safety for Pyrogallol under the intended conditions of use in cosmetic formulations.

TABLES

Table 1. Chemical properties

Property	Value	Reference
	Pyrogallol	
Physical Form	White, odorless crystals	[2]
Molecular Weight (g/mol)	126.1	[2]
Specific Gravity (@ 25 ºC)	1.45 - 1.50	[2]
Vapor pressure (mmHg @ 167.7 ºC)	10	[2]
Melting Point (ºC)	131 - 133	[2]
Boiling Point (ºC)	309	[2]
Water Solubility	Readily soluble	[2]
Other Solubility	Readily soluble in ethanol or ether. Slightly soluble in benzene or chloroform	[2]
log P_{ow}	0.97 (estimated)	[5]

Table 2. Frequency and concentration of use of Pyrogallol according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use
	RLD (2025)[8,9]	% (2025)[10]
Totals*	**20**	**NR†**
summarized by likely duration and exposure**		
Duration of Use		
Leave-On	*18*	*NR*
Rinse-Off	*2*	*NR*
Diluted for (Bath) Use	*NR*	*NR*
Unknown	*NR*	*NR*
Exposure Type		
Baby Products	NR	NR
Children's Makeup	NR	NR
Eye Area	17	NR
Incidental Ingestion	NR	NR
Mucous Membrane	NR	NR
Incidental Inhalation-Spray	NR	NR
Incidental Inhalation-Airbrush	NR	NR
Incidental Inhalation-Powder	NR	NR
Dermal Contact	5	NR
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	NR
Hair-Coloring	2	NR
Nail	3	NR
Other Preparations (Unknown Exposure Type)	NR	NR
as reported by product category		
Eye Makeup Preparations (other than children's eye makeup preparations)		
False Eyelashes	10	NR
Eyelash and Eyebrow Adhesives, Glues, and Sealants	4	NR
Other Eye Makeup Preparations	1	NR
Hair Coloring Preparations		
Eyelash and Eyebrow Dyes	2	NR
Manicuring Preparations		
Nail Polishes and Enamels	3	NR

NR – not reported

† No uses reported, but manufacturers indicated that Pyrogallol is a component of some plant extracts and may be found in cosmetics in low concentrations as an incidental ingredient.

* 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)

Table 3. Genotoxicity studies

Ingredient	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VITRO						
Gene Mutation						
Pyrogallol in 3 hair gel formulations; concentration up to 1.5% w/w	648, 1080, 1800, 3000, or 5000 µg/plate	in formulation at pH of 3.5 - 4.0	*S. typhimurium* strains TA98, TA100, TA102, TA1535, TA1537	Ames test; with and without metabolic activation	Not mutagenic, with or without metabolic activation	[20]
Pyrogallol	3, 10, 33, 100, or 333 µg/plate	not reported	*S. typhimurium* strains TA98 and TA100	Ames test; with or without metabolic activation	Mutagenic in strain TA100, with and without metabolic activation; not mutagenic in strain TA98, with or without metabolic activation	[17]
Pyrogallol	1, 10, or 100 nmol/plate, 1, 2, 4, 6, 8, or 10 µmol/plate	not reported	*S. typhimurium* strains TA98, TA100, TA102	Ames test, with and without metabolic activation	Mutagenic to TA100 with and without metabolic activation; mutagenic to TA98 and weakly mutagenic to TA102 without metabolic activation	[18]
Pyrogallol	56 µg/plate	DMSO	*S. typhimurium* strains TA97, TA98, TA100	Ames test; with and without metabolic activation	Mutagenic in strain TA100 without metabolic activation, negative with metabolic activation; mutagenicity not observed in other strains, with or without metabolic activation	[21]
Pyrogallol	up to 500 µg/plate	details not provided	*S. typhimurium* strains TA97, TA98, TA100	Ames test; with and without metabolic activation	Mutagenic to strains TA97 and TA100; effects were reduced slightly by treatment with chlorine or nitrite	[3]
Pyrogallol	10 - 5000 µg/plate	water or DMSO	*S. typhimurium* strains TA102 and TA2638; *E. coli* strains WP2/pkM101 and WP2 *uvrA*/pKM101	Ames test; without metabolic activation	Mutagenic in all strains tested; toxicity observed at concentrations over 625 µg/plate	[19]
Pyrogallol	10 - 1000 µg/plate	not reported	*S. typhimurium* strains TA 98 and TA100; *E. coli* strain WP2 *uvrA*/pKM101	Ames test; with metabolic activation	Mutagenic in all strains tested with both *S. typhimurium* strains and the *E. coli* strain without metabolic activation; the *E. coli* strain was mutagenic with metabolic activation, but the results for the *S. typhimurium* strains with metabolic activation were equivocal	[17]
Chromosomal Damage						
Pyrogallol at pH 6.0, 7.4, and 8.0	0, 20, 40, 60, or 80 µM	not reported	Chinese hamster V79 cells	Chromosomal aberration test	Clastogenic in a pH-dependent manner; at pH 6.0, Pyrogallol significantly increased the level of chromosomal aberrations at 60 and 80 µM; at pH 7.4 and 8.0, Pyrogallol induced significant levels of chromosomal aberrations at < 80 µM; significant induction of multi-aberrant cells was observed in a pH-dependent manner; the researchers noted that results suggest the genotoxicity of Pyrogallol is almost exclusively mediated by ROS	[22]
DNA Strand Breaks						
Pyrogallol	15 µg/ml	not reported	p53R human cells	Neutral comet assay; cells treated with test material for 30 min; positive control was 0.03% hydrogen peroxide	DNA double-strand breaks were observed	[23]
Pyrogallol	5, 15, or 30 µg/ml	not reported	p53R human cells	p53R assay; cells plated with test material for 18 h; a luciferase assay was then performed	A 30-fold increase in p53-responsive luciferase activity was observed at 15 µg/ml (concentration at the maximal response)	[23]

Table 3. Genotoxicity studies

Ingredient	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VIVO						
Chromosomal Damage						
Pyrogallol in 3 hair gel formulations; concentration up to 1.5% w/w	2000 mg/kg bw	tested neat in formulation	10 male Swiss mice	Micronucleus test; dosed orally with test material and killed 48 h later; bone marrow was extracted from the femur	Not genotoxic; equal numbers of micronucleated polychromatic erythrocytes were detected between the cells of each treated group and the negative control	[20]
Pyrogallol	0, 39, 78, or156 mg/kg	phosphate-buffered saline	groups of 5 male B6C3F1/N mice	Micronucleus test; mice received intraperitoneal injections of the test material once daily for 3 d; mice killed 24 h after last injection; negative and positive controls were utilized	No significant increases in the frequencies of micronucleated polychromatic erythrocytes were observed in the bone marrow; controls yielded expected results	[17]
Pyrogallol	0, 38, 75, 150, 300, or 600 mg/kg	95% ethanol	groups of 5 male and 5 female B6C3F1/N mice	Micronucleus test; mice received test material dermally for 3 mo (see Subchronic Toxicity) section	No significant increases in the frequencies of micronucleated erythrocytes observed in peripheral blood of female mice; in male mice, however, results were judged to be equivocal, based on a significant increase in micronucleated erythrocytes observed at a single dose level (300 mg/kg) at the end of the 3-mo study period	[17]

Table 4. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population/System	Protocol	Results	Reference
IRRITATION						
IN VITRO						
Pyrogallol	25 µl water for wetting test material	25 mg	EpiDerm™ reconstructed epidermis of normal human keratinocytes	MTT assay performed in accordance with OECD TG 431; test material applied to 2 tissue replicates for 3 or 60 min prior to rinsing with phosphate buffer saline and transferring to MTT for 3 h	predicted to be corrosive	[4]
Pyrogallol	1 ml MTT solution	25 mg	reconstructed human epidermis of normal human keratinocytes	human skin model performed in accordance with OECD TG 439; test material applied to 3 tissue replicates for 60 min prior to rinsing with phosphate buffer saline; tissues were transferred to fresh medium and incubated for 42 h before being transferred to MTT for 3 h	predicted to be irritating	[4]
ANIMAL						
Pyrogallol	acetone:olive oil (4:1)	0.125, 0.25, 1, 5, or 10%	groups of 8 female BALB/c mice	irritancy assay; prior to treatment, ear thickness measurements were obtained for each mouse ear; mice received 12.5 µl of test material, vehicle, or positive (DNFB) control on both side of each ear for 4 consecutive days; naïve animals left untreated; 24 h after final treatments, ear thickness measurements were obtained	Pyrogallol induced a positive irritation response at concentrations as low as 0.125%; controls yielded expected results	[44]
SENSITIZATION						
(Q)SAR						
Pyrogallol	not applicable	not applicable	not applicable	Danish (Q)SAR prediction software	predicted to cause allergic contact dermatitis	[4]
ANIMAL						
Pyrogallol	acetone:olive oil (4:1)	study 1 - induction: 0.25, 1, or 5%; challenge: 0.25% study 2 - induction: 1 or 5%; challenge: 0.5%	groups of 8 female BALB/c mice	mouse ear swelling test; 50 µl of test material, DNFB, or vehicle applied to shave lumbar surface of each animal on days 1, 2, and 3; thickness of right ear of each mouse measured 5 d following last exposure; at challenge phase, mice were exposed on dorsal side of right ear pinna with 25 µl of test material or one of the controls; measurements of ear thickness were made 24, 48, and if needed, 72 h after challenge application	In study 1, no significant difference when the naïve, vehicle, or 3 Pyrogallol test groups were compared to the vehicle irritancy control at 24 or 48 h post-challenge. In study 2, a significant increase in percent ear swelling was observed at 72 h post-challenge in mice induced with 5% Pyrogallol	[44]
Pyrogallol	acetone:olive oil (4:1)	study 1: 2.5-50% study 2: 0.5-2.5% study 3: 0.25-10%	groups of 8 female BALB/c mice	LLNA; mice were treated for 3 consecutive days with test material (25 µl), vehicle, or positive (DNFB) control on the dorsum of each ear. Mice were killed and the auricular lymph nodes were excised on day 6 of the study for analysis.	In study 1, Pyrogallol induced a significant increase in the proliferation of lymph node cells (SI > 3) at all concentrations. In study 2, Pyrogallol also induced significant increases in proliferation of lymph node cells at each concentration; however, the low concentration (0.5%) did not reach an SI > 3. In study 3, all test groups, except 0.25% but including the 0.5% group, had a significant increase in the proliferation of lymph node cells when compared to the vehicle controls	[44]

Table 5. Retrospective studies

# Patients	Clinical Testing Type	Location	Years	Results	Reference
261	Retrospective study of patients with contact dermatitis; patients patch tested with Gruppo Italiano Riverca Dermatiti da Contatto e Ambientali (GIRDCA) standard series and with a hairdressers screening series. Pyrogallol tested at 1% in pet.	Italy	1985 to June 1990	Sensitization rate to Pyrogallol was 2.3%	[45]
475	Retrospective study of patients from 5 European centers with contact allergy to cosmetic ingredients	Belgium, United Kingdom, Germany	January to April 1996	Sensitization to Pyrogallol was reported in 1 patient	[46]
19	In a retrospective study of sensitization to resorcinol, a portion of the patients were tested with 1% Pyrogallol in pet.	France	1992 to 1999	Sensitization to Pyrogallol was reported in 9 patients	[49]
628	Retrospective, multicenter study of patients with suspected allergic contact dermatitis of the scalp. Patients were patch tested with 1% Pyrogallol	Austria, Germany, Switzerland	1993 to 2003	Sensitization to Pyrogallol was 5.4%	[47]
666	Retrospective study of patients with suspected hair dye-related allergic contact dermatitis. Patients were patch tested using the European baseline series and an extended hairdresser series, which contained Pyrogallol (concentration tested not reported)	Greece	2006 to 2023	Sensitization to Pyrogallol was 1.54%; cross-reactivity of Pyrogallol positive patients to *p*-phenylenediamine was 100% ($p < 0.001$) and to *p*-toluenediamine was 90.9% ($p < 0.001$)	[48]

Table 6. Assessment of effects in persons occupationally exposed to Pyrogallol

Occupation	Study methods	Study results	Reference
54 female hairdressers	Study of the occurrence and cause of hairdressers/ occupational skin and respiratory diseases in Finland; from a random sample of 500 hairdressers, 355 were interviewed February - April 1994 and of these, 54 were selected for patch testing with a modified European standard series, a hairdressers' series, and a combined cosmetic, preservative, and perfume series; Pyrogallol was included in testing (concentration and vehicle not reported)	None of the hairdressers that underwent patch testing had positive reactions to Pyrogallol	[50]
302 hairdressers	Study using data from 9 Italian centers by the GIRDCA on hairdressers with dermatitis from January 1985 to June 1990. Patients were patch tested according to International Contact Dermatitis Research Group (ICDRG) recommendations using Finn chambers on Scanpor tape. Pyrogallol was tested at 1% in pet.	1.3% of patients had positive reactions to Pyrogallol	[51]
809 hairdressers	Study using data from 9 European centers on hairdressers with hand eczema from 1988 to 1991 (with exception to 3 centers). Pyrogallol was tested at 1% in pet.	0.8% of patients had positive reactions to Pyrogallol	[52]

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6
Final Report on the Safety Assessment of Pyrogallol

Pyrogallol, a benzenetriol, is used in oxidative hair dyes at concentrations ranging from ≤0.1 to 5.0%. The oral LD_{50}'s in rats ranged from 800 to 1270 mg/kg. Pyrogallol was not an ocular irritant when tested at a concentration of 1%. It was slightly irritating and induced sensitization reaction in the skin of guinea pigs. Sensitization reactions were noted in 3 of 25 patients patch tested with Pyrogallol.

Significant teratogenic effects were not observed in the offspring of female rats dosed with Pyrogallol. No treatment-related effects were observed in a multigeneration reproductive toxicity study in which rats received dermal applications of a hair dye containing 0.4% Pyrogallol.

Pyrogallol was mutagenic in almost all systems tested. However, in two carcinogenicity studies, the number of neoplasms in mice dermally treated with 50% Pyrogallol in acetone was not significantly different from that of controls. Similar results were reported in a carcinogenicity study in which a hair dye containing 0.49% Pyrogallol and H_2O_2 in aqueous solution was applied to the skins of mice.

On the basis of the available animal and clinical data presented in this report, it is concluded that Pyrogallol is safe as a cosmetic ingredient in the present practices of use and concentration.

INTRODUCTION

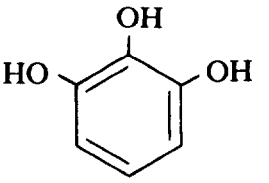
The toxicity of Pyrogallol, a benzenetriol, is reviewed in this report. The Cosmetic Ingredient Review Expert Panel has evaluated the safety of the following benzenediols: 2-Methyl Resorcinol, Resorcinol, Hydroquinone, and Pyrocatechol.[1,2]

CHEMISTRY

Chemical and Physical Properties

Pyrogallol: Pyrogallol (CAS No. 87-66-1) is an aromatic alcohol with the following structure[3]:

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As a cosmetic ingredient, Pyrogallol consists of a minimum of 99% Pyrogallol.[4] Other names for this ingredient are: 1,2,3-Benzenetriol, 1,2,3-Trihydroxybenzene, and Pyrogallic acid.[3,5] Technical synthetic and technical natural grades of Pyrogallol are available. Technical synthetic Pyrogallol contains 90 to 96% w/w Pyrogallol, and technical natural Pyrogallol contains not less than 98% Pyrogallol.[6] Pyrogallol is stable in the dark and in the absence of alkali,[4] and sublimes when heated slowly.[7] It is oxidized easily when in alkaline solutions, and such solutions of Pyrogallol are potent reducing agents.[8] A UV spectral analysis of chemically pure (99%) Pyrogallol, 0.1% w/v in methanol, showed a single absorbance maximum at 267.5 nm.[9] Additional properties of Pyrogallol are listed in Table 1.

TABLE 1. PROPERTIES OF PYROGALLOL

Property	*Description*	*Reference*
Molecular weight	126.11	10
Form	White crystals	7
Odor	None	7
Solubility	Readily soluble in water, ethanol, or ether. Slightly soluble in benezene or chloroform	4
Boiling point	309°C	7
Melting range	131–133°C	7
Specific Gravity (25°C)	1.45–1.50	4
Refractive index	1.561	10
Vapor pressure	10 mm at 167.7°C	11
Residue on ignition	0.1% max	4

Methods of Production

Pyrogallol is prepared via the chlorination of cyclohexanol to tetrachlorocyclohexanone, followed by hydrolysis.[4]

Analytical Methods

Pyrogallol has been assayed via the following methods: thin layer chromatography,[12–15] gas chromatography,[16] gas-liquid chromatography, high performance liquid chromatography, ultraviolet spectrophotometry, and mass spectrometry.[15]

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Impurities

Iron (0.001%) and heavy metals (5 ppm max) are impurities that have been detected in Pyrogallol.[4] Data on possible organic impurities in cosmetic grade Pyrogallol, such as chlorinated aromatic hydrocarbons, are not available.

USE

Purpose in Cosmetics

Pyrogallol was the first synthetic organic dye to be used on human hair.[7] It is being used at present as a modifier in oxidation dyes.[4] Typical use concentrations of Pyrogallol in oxidative hair dyes range between 0.25 and 0.383% by weight.[8]

Scope and Extent of Use in Cosmetics

The FDA cosmetic product formulation computer printout[9] is compiled through voluntary filing of such data in accordance with Title 21 Part 720.4 of the Code of Federal Regulations.[20] Ingredients are listed in preset concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product. The actual concentration would be a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges provide 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. Pyrogallol is present in 42 hair dyes and colors (all types requiring caution statement and patch test) at concentrations ranging from ≤0.1 to 5.0% (Table 2).[19]

In countries of the European Economic Community, the maximum concentration of Pyrogallol allowed in hair dyes (for professional or general use) is 5.0%.[21] Pyrogallol (Quasi Drug Use Only) has also been approved for use in cosmetic formulations marketed in Japan.[22]

Hair coloring formulations containing Pyrogallol are applied to or may come in contact with hair, skin (particularly the scalp), eyes, and nails. These formulations may be used as often as once per week.

TABLE 2. PRODUCT FORMULATION DATA[19]

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*		
			>1–5	*>0.1–1*	*≤0.1*
Pyrogallol					
Hair dyes and colors	1164	42	1	22	19
1989 Totals		42	1	22	19

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The oxidative or permanent hair dyes containing Pyrogallol, as "coal tar" hair dye products[23] are exempt from the principal adulteration provision and from the color additive provision in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act of 1938 when the label bears a caution statement and "patch test" instructions for determining whether the product causes skin irritation.[24] In order to be exempt, the following caution statement must be displayed on all coal tar hair dye products:

> Caution—This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should be made. This product must not be used for dyeing the eyelashes or eye-brows; to do so may cause blindness.

Patch test instructions call for a 24-h patch on the skin of the user with the intermediates and hydrogen peroxide mixed in the same manner as in use. This test is to be performed prior to each and every application of the hair dye.[25]

Noncosmetic Use

Pyrogallol may be used safely in combination with ferric ammonium citrate for coloring plain and chromic catgut sutues used in general and ophthalmic surgery. The concentration of the ferric ammonium citrate–pyrogallol complex shall not exceed 3.0% of the total weight of the suture material.[20] Other uses of Pyrogallol are: developer in photography, making colloidal solutions of metals, mordant for wool, staining of leather, process engraving, manufacture of various dyes, manufacture of pesticides, dying furs, reagent for antimony and bismuth (in analytical chemistry), and active reducer for gold, silver, and mercury salts.[7,26]

BIOLOGICAL PROPERTIES

Pyrogallol inhibited rat thyroid peroxidase activity and the uptake and incorporation (into tyrosine) of ^{125}I in rat thyroid slices *in vitro*.[27] Other effects of Pyrogallol are summarized as follows: negative chronotropic effect on perfused rabbit and frog hearts and blood pressure elevation in dogs,[28] increased cardiac output and alveolar-ventilation in normal sheep and sheep suffering from respiratory distress,[29] uncoupling of oxidative phosphorylation in rat kidney and beef heart mitochondria *in vitro*,[30] decreased ATP concentrations in mouse brain,[31] inhibition of catechol-O-methyl transferase activity,[32] inhibition of rat liver mitochondrial aldehyde dehydrogenase *in vitro*,[33] and inhibition of beef heart mitochondrial succinoxidase and NADH-oxidase enzyme systems.[34]

Absorption, Distribution, Metabolism, and Excretion

Pyrogallol (100 mg/kg) was administered to 4 adult albino rats (weight 250–350 g) via either stomach tube or intraperitoneal injection. Urine samples were collected 24 h after administration, extracted with ether, and analyzed via thin layer chromatography. Some of the urine samples were subjected to acid hydrolysis before extraction. Pyrogallol was not detected in extracts of nonhydrolyzed urine. However, prominent spots, corresponding to Pyrogallol and 2-O-methylpyrogallol, were observed on

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chromatograms of hydrolyzed urine extracts. Additionally, traces of resorcinol were detected in these extracts. Resorcinol also was detected in rat fecal extracts that had been incubated with Pyrogallol, indicating that Pyrogallol could have been metabolized to resorcinol.[35] Results from guinea pig liver perfusion experiments indicated that Pyrogallol was conjugated with glucuronic acid. Glucuronic acid conjugates were detected in blood and urine via thin layer chromatography.[36] Pyrogallol in urine from humans[37] probably is derived from the decarboxylation of gallic acid, an ingredient in tea, in the alimentary tract.

Female mice (weights 20–25 g, number not stated) of an inbred strain were injected intraperitoneally with Pyrogallol (60 mg/kg). Concentrations of Pyrogallol in the brain were determined according to a modification of the procedure by Swain and Hillis.[38] The maximum concentration of Pyrogallol in the brain, 28.4 μg/wet weight of brain, was noted 10 min after injection. At 15 min postinjection, the concentration of Pyrogallol approached zero.[31]

TOXICOLOGY

Acute Oral Toxicity

The oral toxicities of technical synthetic Pyrogallol (92.2% w/w Pyrogallol) and technical natural Pyrogallol (98.8% w/w Pyrogallol) were evaluated using 54 male rats (weight 249–305 g) and 60 female rats (weight 191–240 g) of the Sprague-Dawley strain. Both test substances were diluted to a concentration of 500 mg/ml of distilled water, and the following doses were administered via gavage: 800 to 2261 mg/kg (natural Pyrogallol, 24 male rats), 566 to 1600 mg/kg (natural Pyrogallol, 24 female rats), 566 to 1600 mg/kg (synthetic Pyrogallol, 24 male rats), and 283 to 1131 mg/kg (synthetic Pyrogallol, 30 female rats). Six male and 6 female control animals were dosed with 4.5 ml of distilled water/kg of body weight. The oral LD_{50}'s for male and female rats dosed with technical synthetic Pyrogallol were 1270 mg/kg (95% confidence limits = 1054–1330 mg/kg) and 800 mg/kg (95% confidence limits = 664–964 mg/kg), respectively. Oral LD_{50}'s for male and female rats dosed with technical natural Pyrogallol were 1270 mg/kg (95% confidence limits = 839–1923 mg/kg) and 848 mg/kg (95% confidence limits = 733–982 mg/kg), respectively.[6]

In another study, the acute oral toxicity of a 50% solution of Pyrogallol (in DMSO) was evaluated using 10 male Sprague-Dawley rats. The LD_{50} was 1800 mg/kg (95% confidence limits: 1420–2290 mg/kg).[39]

The oral toxicity of Pyrogallol was evaluated using 5 deer mice (average weight 20 g). Twenty-five wheat seeds, treated with 2.0% (w/w) Pyrogallol, were placed in the cage of each mouse daily for 3 days. The number of wheat seeds consumed daily was recorded, and the total number of treated seeds consumed by all mice during the 3-day period was substracted from the total number of seeds available. The difference was converted into what was termed the feed reduction (FR), defined as the percentage of seeds refused. The FR, average weight of individual wheat seeds (50 mg), and average weight of each mouse (20 g) were used to calculate the LD_{fr}. The LD_{fr} represented the average amount of Pyrogallol (mg/kg/day) ingested without inducing > 50.0% mortality. The LD_{fr} for Pyrogallol was 1240 mg/kg/day.[40]

Pyrogallol also was administered, in the diet, to three groups of 1-day-old chicks (10/group) for 4 weeks. The three groups were fed basal diets containing 0.1, 1.0, and

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2.0% Pyrogallol, respectively. Group mortality rates for animals fed 0.1%, 1.0%, and 2.0% Pyrogallol were 0.0%, 10.0%, and 95.0%, respectively. Deaths in the 2.0% group occurred within 10 days.[41]

Acute Dermal Toxicity

The dermal toxicity of technical synthetic Pyrogallol (92.2% w/w Pyrogallol) and technical natural Pyrogallol (98.8% w/w Pyrogallol) was evaluated using 18 male (weight 244–309 g) and 18 female (weight 200–238 g) Sprague-Dawley rats. Each test substance was diluted with distilled water to a concentration of 500 mg/ml and applied (dose = 2100 mg/kg) via occlusive patches to the backs of 6 male and 6 female animals. Patches remained for 24 h. A control group of 12 rats was treated with distilled water according to the same procedure. An LD_{50} could not be determined for either test substance at the administered dose.[42]

Subchronic Percutaneous Toxicity

The percutaneous toxicity of a hair dye formulation containing 0.4% Pyrogallol was evaluated using 12 (6 males, 6 females) adult New Zealand white rabbits. The hair dye was mixed with an equal volume of 6.0% hydrogen peroxide and applied (1 ml/kg) to the dorsolateral aspects of the thoracic–lumbar area twice per week for 13 weeks. Hair was clipped from application sites throughout the study. The application sites on 6 animals were abraded on the first day of each week of treatment. Application sites on all animals were shampooed, rinsed, and dried 1 h after application of the dye. Three groups of untreated rats (12/group) served as controls. Analyses of blood and urine were done during weeks 0, 3, 7, and 13. Animals were killed after the 13th week, and both gross and microscopic examinations were performed. Slight thickening of the skin was observed only at sites where the dye had been applied. There were statistically significant differences in clinical chemistry and hematological values between experimental and control groups. The results of the urinalyses were unremarkable. Neither gross nor microscopic changes related to administration of the dye were observed.[43]

Immunotoxicity

The immunosuppressive potential of Pyrogallol was evaluated using the Mishell-Dutton system. In this *in vitro* system, B lymphocyte cultures from dissociated mouse splenic cells were incubated with sheep red blood cells (antigens) for 5 days. The B lymphocytes mature into cells that produce antibodies directed against sheep red blood cells. These antibodies (along with complement) cause lysis of erythrocytes, indicated by a zone of lysis (or plaque) around the antibody-forming cells. The addition of Pyrogallol (5 μg/culture) resulted in ≥ 90% suppression of plaque formation. Toxicity, determined by trypan blue dye exclusion, was expressed as the test substance dose (μg/culture) resulting in a 50% reduction in viability. Pyrogallol induced toxicity at a dose of 5 μg/culture. In control cultures, the number of plaque-forming cells per culture ranged from 10,000 to 25,000.[44]

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Cytotoxicity

The effect of Pyrogallol on plasma membrane integrity was evaluated using human diploid embryonic lung fibroblasts (cell line MRC-5). Plasma membrane damage was quantified by the leakage of a cytoplasmic nucleotide marker from radioactive cells. Fibroblasts containing ^{3}H-uridine were rinsed with salt solution and then treated with Pyrogallol for 30 min. Pyrogallol was added to cell cultures as a 25 mM solution, made from ethanol or dimethyl sulfoxide stock solutions by dilution with Tris-buffered saline. Cultures were then centrifuged, and the released radioactivity was measured. Results were expressed as percentages of the maximal amount of radioactivity released. There was no evidence of plasma membrane damage.[45]

The effect of Pyrogallol on ciliary activity was evaluated using tracheal organ cultures prepared from 16 to 17-day-old chicken embryos. One tracheal ring was placed in a Plexiglas chamber that contained culture medium admixed with either ethanol or dimethyl sulfoxide solutions of Pyrogallol. The concentration of Pyrogallol was 5 mM. Ciliary activity was recorded (60 min period) using an inverted microscope connected to a TV camera, TV monitor, and videotape recorder. This procedure was repeated on at least three different occasions, using rings from different tracheal preparations. Ciliostasis was noted after 15 min of observation.[46]

Ocular Irritation

The ocular irritation potential of Pyrogallol was evaluated using two groups of 6 male New Zealand white rabbits (weight 2.5–3.0 kg). In one group of animals, the test substance (100 mg, powder form) was instilled into the conjunctival sac of the left eye. In the other group, 0.1 ml of a 1.0% solution of Pyrogallol (in propylene glycol) was instilled into the left eye. Eyes (both groups) were not rinsed after instillation. Untreated eyes served as controls. Pyrogallol (powder form) induced ocular irritation, although the 1.0% solution of Pyrogallol was not an ocular irritant.[47]

Skin Irritation

The primary skin irritation potential of Pyrogallol was evaluated using 6 albino rabbits. The test substance (500 mg, powder form) was applied to abraded and intact skin sites on each animal. Each site was covered for 24 h with a patch (type not stated) secured with adhesive tape. Reactions were scored 24 and 72 h after patch application. A primary irritation index of 0.5 was reported.[48]

A skin irritation study of technical synthetic Pyrogallol (92.2% w/w Pyrogallol) and technical natural Pyrogallol (98.8% w/w Pyrogallol) was conducted using 6 Dunkin Hartley female guinea pigs (weight not < 350 g). Each test substance was diluted with distilled water to a concentration of 500 mg/ml and applied to two sites (0.05 ml/site) on the back of each animal via patches made of lint. The four patches (two per test substance) were covered with aluminum foil and held in place with waterproof plaster for 24 h. Sites were then washed with soap and water, rinsed, and dried. Each site was graded 1, 4, 24, 48, and 72 h after patch removal according to the scales: 0 (no erythema) to 4 (severe erythema to slight eschar formation) and 0 (no edema) to 4 (severe edema, raised more than 1 mm and extending beyond area of exposure). Very slight erythema was observed at one site treated with technical natural Pyrogallol (3 guinea pigs), and at one site treated with technical synthetic Pyrogallol (2 guinea pigs).

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Additionally, dryness and thickening (leading to flaking) of the skin were observed at all treated sites (between 4 and 8 days after patch removal), except for one site treated with technical natural Pyrogallol and one site treated with technical synthetic Pyrogallol (same guinea pig). Both test substances were classified as slightly irritating to guinea pig skin.[49]

Skin Sensitization

The skin sensitization potential of unrefined Pyrogallol was evaluated using 29 female Hartley guinea pigs (average body weight 350 g). On three consecutive days, 0.1 ml volumes of 0.01 M Pyrogallol and 0.05 M Pyrogallol (solutions contained NaCl and a complete adjuvant) were injected subcutaneously into the feet of 21 guinea pigs. During the same week, a fourth injection was made at a site near the neck. Test solutions also were injected subcutaneously 4 weeks after the first injection. The remaining 8 guinea pigs were injected subcutaneously with 0.01 and 0.1 M Pyrogallol according to the same induction procedure. However, the challenge phase consisted of sealed cloth applications of test solutions. Injection sites on each animal were examined macroscopically and microscopically. Of the 21 guinea pigs tested, 7 and 14 animals had sensitization reactions to 0.01 M Pyrogallol and 0.05 M Pyrogallol, respectively. Of the remaining 8 guinea pigs, 3 and 6 animals had sensitization reactions to 0.01 M and 0.1 M Pyrogallol, respectively.[50]

In another study, the skin sensitization potential of Pyrogallol was evaluated using groups of 10 female Hartley albino guinea pigs. During induction, 0.05 ml of a 1.0% solution of Pyrogallol (in water) was injected intradermally. A 25.0% solution of the test substance (in propylene glycol) was applied topically 1 week later. Each site was covered with an occlusive patch for 48 h. After a 2-week nontreatment period, the animals were challenged with a single topical application of the 25.0% solution. There was no evidence of sensitization in any of the animals tested.[51]

Reproductive Effects

A multigeneration reproduction study was conducted using Charles River CD rats. A total of 40 males and 40 females were tested with a hair dye formulation that contained 0.4% Pyrogallol. The dye was mixed with an equal volume of 6% hydrogen peroxide and applied (0.5 ml) to the skin twice per week throughout mating, gestation, and during the period of lactation to weaning of the F_{1b}, F_{2b}, and F_{3c} litters of the respective generations. There were no treatment-related changes in general behavior and appearance, body weight, or survival in parents or offspring. However, mild skin reactions, in treated animals, were noted intermittently throughout the study. Fertility, gestation, and viability indices were comparable between control and experimental groups. Additionally, there were no treatment-related gross or microscopic lesions observed in F_{1b} parental rats or F_{3b} weaning rats.[52]

Teratogenicity

Pyrogallol (in propylene glycol) was administered via gavage to 17 female Sprague-Dawley rats (weight 225–250 g) on days 6 to 15 of gestation. The following doses were administered: 100 mg/kg (5 rats), 200 mg/kg (6 rats), and 300 mg/kg (6 rats). Solutions

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of Pyrogallol were prepared daily and dosed at a rate of 10 ml/kg. Animals in the vehicle control group (22 rats) were dosed with propylene glycol at a rate of 10 ml/kg. Vitamin A and aspirin were administered to positive control groups on day 9 of gestation and days 6 to 15 of gestation, respectively. Vitamin A was administered at a dose of 100,000 IU per animal, and aspirin was administered at a dose of 350 mg/kg. All dams were killed on day 20 of gestation via carbon dioxide inhalation. There were no mortalities in experimental or vehicle control groups during the gestational period. However, a significant decrease in the mean maternal weight gain occurred (days 6–16 of gestation) in rats that received 300 mg/kg doses of Pyrogallol. Smaller fetuses and a significant increase in the total number of fetal resorptions also were noted in this group. The numbers of fetal implantations and fetal anomalies in all experimental groups were not significantly different from those in the vehicle control group. A statistically significant increase in the number of abnormal fetuses with gross, soft tissue, and skeletal anomalies ($p = 0.001$) was observed in groups dosed with vitamin A or aspirin.[53]

The teratogenicity of a hair dye formulation containing 0.4% Pyrogallol was evaluated using 20 Charles River CD female rats. The hair dye (2 ml/kg) was applied to the dorsoscapular area (shaved skin) of each animal on days 1, 4, 7, 10, 13, 16, and 19 of gestation. Three groups of untreated rats (unshaved) served as controls. Animals in the positive control group were given acetylsalicylic acid (250 mg/kg) via gavage on days 6 to 16 of gestation. The dams were killed on day 20 of gestation via chloroform anesthesia, and fetuses were removed via cesarean section. One third of the fetuses from each litter were examined for visceral anomalies. The remaining fetuses were examined for skeletal anomalies. Toxic effects were not observed in experimental or control dams throughout the study. The mean numbers of corpora lutea, implantation sites, and live fetuses in experimental groups were not significantly different from those in control groups. There were also no significant differences in the number of females with resorption sites and the mean number of resorptions per pregnancy. The incidence of fetal soft tissue and skeletal anomalies in experimental groups was not significantly different from that of negative control groups. A significant increase in the number of fetuses with skeletal and soft tissue anomalies and in the number of dead or resorbed fetuses was observed in the positive control group.[43]

MUTAGENICITY

In Vitro Tests

The mutagenic potentials of technical natural Pyrogallol (not < 98% w/w Pyrogallol) and technical synthetic Pyrogallol (90–96% w/w Pyrogallol) were evaluated using strains TA1535, TA1537, TA1538, TA98, and TA100 of *Salmonella typhimurium*. Both test substances were diluted with water and tested at concentrations that ranged from 50 to 5,000 μg/plate (technical natural Pyrogallol) and 15 to 5000 μg/plate (technical synthetic Pyrogallol) according to the procedure by Ames et al.[54] Both grades of Pyrogallol were mutagenic to strains TA1537 and TA100 in both the presence and absence of metabolic activation (Table 3).[55]

In another study, the mutagenicity of Pyrogallol was evaluated using the strains of *S. typhimurium* stated above. Tests were conducted with and without metabolic activation.[54] Pyrogallol was tested at concentrations up to 3600 μg/plate. In the absence of metabolic activation, Pyrogallol was mutagenic to strain TA1537. Pyro-

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gallol was mutagenic to strains TA98 and TA100 with and without metabolic activation (Table 3).[56]

The mutagenicity of Pyrogallol (in DMSO) was evaluated using strains TA1538 and TA98 of *S. typhimurium*. Concentrations ranging from 20 to 1000 μg/plate were tested with and without metabolic activation.[54] With metabolic activation, Pyrogallol was not mutagenic to strain TA98. Without metabolic activation, a weak mutagenic response to Pyrogallol (500 μg/plate) was observed in strain TA98. However, there was no linear correlation between mutagenicity and doses tested. Pyrogallol was not mutagenic to strain TA1538 with or without metabolic activation (Table 3).[53]

In another study, the mutagenicity of Pyrogallol (in water) was evaluated using strains TA98, TA100, and TA1537 of *S. typhimurium*. Concentrations ranging from 5 to 200 μg/plate were tested.[54] The 200 μg/plate concentration was tested with and without metabolic activation. Concentrations less than 200 μg/plate were tested without metabolic activation. Pyrogallol was mutagenic to strains TA100 and TA1537 with and without metabolic activation but was not mutagenic to strain TA98 (Table 3).[57]

The mutagenicity of Pyrogallol (in water) was evaluated using strain TA100 of *S. typhimurium*. Pyrogallol was tested at a concentration of 100 μg/plate according to a modification of the procedure by Ames et al.[54] Without metabolic activation, Pyrogallol was described as being moderately mutagenic to strain TA100. With metabolic activation, Pyrogallol was considerably mutagenic to strain TA100 (Table 3).[58]

The Ames test was used to evaluate the mutagenic potential of Pyrogallol in strains TA98, TA100, and TA1537 of *S. typhimurium*. With and without metabolic activation, Pyrogallol was mutagenic to strains TA98 and TA100 within the range of concentrations tested (0.1–15.0 μmol/plate). In the spot test, Pyrogallol was mutagenic to strain TA1537 (Table 3).[59]

The mutagenicity of Pyrogallol (in ethanol) was evaluated using strains TA98, TA100, TA1535, and TA1537 of *S. typhimurium*. Tests were conducted with and without metabolic activation.[54] In spot tests, Pyrogallol (3 μmol/plate) was not mutagenic to strains TA1535 and TA1537 with or without metabolic activation. The mutagenicity of Pyrogallol in strains TA98 and TA100 was questionable. In quantitative plate tests involving strain TA98, Pyrogallol was tested at concentrations ranging from 0.3 to 3.0 μmol/plate. In some of these tests, Pyrogallol was described as being weakly mutagenic to strain TA98 with and without metabolic activation (Table 3).[60]

In the L5178Y mouse lymphoma cell assay, technical synthetic Pyrogallol (in distilled water) was tested at concentrations of 4 to 80 μg/ml. Compared to vehicle control values, Pyrogallol (between 17 and 80 μg/ml) increased the mutation frequencies and absolute mutant numbers in the presence of metabolic activation. Without metabolic activation, results with Pyrogallol (between 19 and 34 μg/ml) were the same. It was concluded that technical synthetic Pyrogallol was mutagenic (Table 3).[61]

Technical synthetic Pyrogallol (in distilled water) was tested for induction of chromosomal aberrations in human lymphocytes cultured *in vitro*. Pyrogallol was tested without metabolic activation at concentrations of 10, 50, 75, and 100 μg/ml and with metabolic activation at concentrations of 100, 500, and 1000 μg/ml. Compared to the solvent control, a significantly higher proportion of cells with chromosomal aberrations was noted in cultures incubated with 50, 75, and 100 μg/ml concentrations (without metabolic activation). The same was true for cultures incubated with concentrations of 500 and 1000 μg/ml (with metabolic activation). It was concluded that

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technical synthetic Pyrogallol was clastogenic with and without metabolic activation (Table 3).[62]

Pyrogallol induced chromatid breaks and exchanges in cultures of Chinese hamster ovary cells (without metabolic activation). With metabolic activation, the chromosome damaging activity of Pyrogallol was suppressed.

Pyrogallol was tested at concentrations of 0.1 mg/ml and 3.0 mg/ml of culture medium, respectively, with and without metabolic activation. Results were based on the analysis of 200 metaphase plates per sample (Table 3).[63]

The mutagenic activity of Pyrogallol in strain D7 of *Saccharomyces cerevisiae* was evaluated using the mitotic gene conversion assay. Pyrogallol was tested at a concentration of 0.3 mg/ml of culture medium. Significant ($P < 0.01$) mitotic gene conversion was noted when the pH of the culture medium was alkaline (pH 10). At pH 7, significant mutagenic activity was not noted (Table 3).[64]

In Vivo Tests

The mutagenicity of Pyrogallol was evaluated using the recessive lethal mutations test. One dose of Pyrogallol (in 5% saccharose) was fed to Berlin K (wild-type) and Basc strains of *Drosophila melanogaster*. The dose administered was close to the LD_{50}. Approximately 1200 X-chromosomes were tested per experiment in each of three successive broods. F_2 progeny cultures with two, or fewer, wild-type males were routinely retested in the F_3 generation to confirm X-linked recessive lethal mutations. Pyrogallol significantly increased ($P = 0.05$) the frequency of sex-linked recessive lethal mutations.[56]

In the micronucleus test,[65] Pyrogallol (252 mg/kg) was administered intraperitoneally to 4 mice at 0 and 24 h. An untreated group of 4 mice served as the control. Bone marrow smears were prepared at 30 h, and 1000 polychromatic erythrocytes were scored per mouse. Compared to the control, Pyrogallol significantly increased ($p < 0.01$) the percentage of micronucleated polychromatic erythrocytes.[56]

In another *in vivo* test, mice (3–4 months old) were injected intraperitoneally with 0.01 M, 0.02 M, and 0.03 M solutions of Pyrogallol. Bone marrow tissue was removed 24 h after administration and prepared for microscopic examination. One-hundred fifty metaphases were counted per slide. Chromatid breaks were observed only in bone marrow cells from mice dosed with 0.02 M and 0.03 M concentrations of Pyrogallol.[39]

CARCINOGENICITY

The carcinogenicity of Pyrogallol was evaluated using 150 female Swiss mice (7 weeks old). Three groups of mice (50/group) were treated with 5%, 25%, and 50% solutions of Pyrogallol (in acetone), respectively. Each solution (0.02 ml) was applied to dorsal shaved skin, between the flanks, twice per week. A total of 135 mice served as the untreated control group. Mice treated with acetone and 7,12-dimethylbenzanthracene served as vehicle and positive controls, respectively. Gross and microscopic examinations were performed. In all treatment groups, the number of neoplasms induced was not significantly different from that of the untreated control group. Lymphomas, pulmonary adenomas, and hepatic hemangiomas predominated. There were no skin neoplasms. At week 100, 13 of the 150 mice of the Pyrogallol groups were

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TABLE 3. IN VITRO MUTAGENICITY TESTS

Test substance	*Concentrations tested*	*Strains tested*	*Procedure*	*Results*	*Reference*
Pyrogallol (≤ 98% w/w)	50–5000 μg/plate	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538	Ames et al.[54]	Mutagenic to strains TA100 and TA1537 (presence and absence of metabolic activation)	55
Pyrogallol (90–96% w/w)	15–5000 μg/plate	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538	Ames et al.[54]	Mutagenic to strains TA100 and TA1537 (presence and absence of metabolic activation)	55
Pyrogallol	Up to 3600 μg/plate	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538	Ames et al.[54]	Mutagenic to strains TA98 and TA100 (presence and absence of metabolic activation) and strain TA1537 (absence of metabolic activation)	56
Pyrogallol (in DMSO)	20–1000 μg/plate	*Salmonella typhimurium* strains TA98 and TA1538	Ames et al.[54]	Not mutagenic to strain TA98 (presence of metabolic activation) and weakly mutagenic to strain TA98 (absence of metabolic activation)	53
Pyrogallol (in water)	5–200 μg/plate	*Salmonella typhimurium* strains TA98, TA100, and TA1537	Ames et al.[54]	Mutagenic to strains TA100 and TA1537 (presence and absence of metabolic activation)	57
Pyrogallol (in water)	100 μg/plate	*Salmonella typhimurium* strain TA100	Ames et al.[54]	Moderately mutagenic (absence of metabolic activation) and considerably mutagenic (presence of metabolic activation)	58
Pyrogallol	0.1–15.0 μmol/plate	*Salmonella typhimurium* strains TA98, TA100, and TA1537	Ames et al.[54]	Mutagenic to strains TA98 and TA100 (presence and absence of metabolic activation)	59
Pyrogallol	0.1–15.0 μmol/plate	*Salmonella typhimurium* strains TA98, TA100, and TA1537	Spot test (Ames et al.[54])	Mutagenic to strain TA1537	59

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Pyrogallol (in ethanol)	3.0 μmol/plate	*Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537	Spot test (Ames et al.[54])	Mutagenicity to strains TA98 and TA100 was questionable	60
Pyrogallol (in ethanol)	0.3–3.0 μmol/plate	*Salmonella typhimurium* strain TA98	Ames et al.[54]	Weakly mutagenic	60
Pyrogallol (in distilled water)	4.0–80.0 μg/ml		L5178Y mouse lymphoma cell assay	Mutagenic (presence and absence of metabolic activation)	61
Pyrogallol (in distilled water)	50, 75 and 100 μg/ml		Chromosome aberrations assay involving human lymphocytes (absence of metabolic activation)	Clastogenic	62
Pyrogallol (in distilled water)	100, 500, and 1000 μg/ml		Chromosome aberrations assay involving human lymphocytes (presence of metabolic activation)	Clastogenic	62
Pyrogallol	0.1 mg/ml		Chromatid breaks and exchanges assay involving Chinese hamster ovary cells	Chromatid breads and exchanges (presence and absence of metabolic activation)	63
Pyrogallol	0.3 mg/ml	*Saccharomyces cerevisiae* strain D7	Mitotic gene conversion assay	Significant mitotic gene conversion at pH 10 but not at pH 7	64

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alive. None of the mice were alive at week 110. Survivors were noted in the control group during the 120th week.[66] In another study (same procedure), the carcinogenicity of Pyrogallol in New Zealand rabbits (8 weeks old) was evaluated. Three groups of 5 rabbits were treated with solutions of 5%, 25%, and 50% Pyrogallol (in acetone or methanol), respectively. Fourteen rabbits served as untreated controls. Positive controls (15 rabbits) were treated with 9,10-dimethylbenz[a]anthracene. After 160 weeks of treatment, the only evidence of tumor formation in experimental groups was a uterine tumor in 1 animal treated with 50% Pyrogallol. A significant number of skin neoplasms (papillomas, squamous cell carcinomas, and keratocanthomas) was observed in the positive control group. Pyrogallol was not carcinogenic at any of the concentrations tested.[67]

Pyrogallol (in 50% DMSO) was administered subcutaneously (0.1 mg/g body weight) to 9 male and 10 female 2-week-old, Fischer rats for 8 weeks. During the next 50 weeks of treatment, the dose was changed to 14 mg/rat. Rats in the control group were dosed with 50% DMSO. In the experimental group, histiocytomas were observed at the injection sites of 3 male rats and 1 female rat. Neoplasms were not observed in controls.[59]

The carcinogenicity of an oxidative hair dye formulation containing 0.49% Pyrogallol was evaluated using random-bred Swiss Webster mice (6 weeks old). The experimental group and the two untreated control groups each contained 60 male and 60 female mice. Treatment was initiated when the mice were 8 weeks old. The dye was mixed with an equal volume of 6% H_2O_2 and applied (0.5 ml per application) once per week for a period of 20 months. Applications were made via a calibrated syringe to an area of skin, clipped free of hair, in the interscapular region. After 9 months of treatment, 10 males and 10 females were selected randomly from each group for clinical tests, hematology, and necropsy. Urine samples were analyzed for color, pH, occult blood, albumin, and glucose. Blood samples were obtained via cardiac puncture, and complete blood counts and differential white cell counts were determined. At 20 months posttreatment, the remaining animals were killed for necropsy. At the time of necropsy, complete and differential cell counts were performed on blood samples from 10 mice (5 males, 5 females) per group. Results from analyses of the blood and urine indicated no treatment-related effects. Pulmonary adenomas, hepatic hemangiomas, and malignant lymphomas were observed in experimental and control groups. Statistical analyses, chi-square and Fisher exact tests, of the incidence of hepatic hemangiomas, pulmonary adenomas, and malignant lymphomas indicated no significant differences between experimental and control groups.[68]

Cocarcinogenicity

The cocarcinogenicity of Pyrogallol was evaluated using 50 female ICR/Ha Swiss mice (6–8 weeks old). Pyrogallol (5 mg in acetone) and benzo[a]pyrene (5 μg/0.1 ml acetone) were applied simultaneously to clipped dorsal skin three times weekly for 440 days. The control group (50 mice) was treated with benzo[a]pyrene according to the same procedure. Tumors (> 1 mm in diameter) persisting for 30 days or more were recorded. Animals with carcinomas were killed when moribund or approximately 2 months after tumors were clinically classified as malignant. All animals were necropsied, and specimens of neoplasms were examined microscopically. Ten of the 50 mice treated with benzo[a]pyrene developed squamous carcinomas, whereas 33 of

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the 50 mice treated with benzo[a]pyrene and Pyrogallol developed squamous carcinomas. No neoplasms were observed in the mice treated with Pyrogallol alone.[69]

CLINICAL ASSESSMENT OF SAFETY

Skin Sensitization

Twenty-five patients (average age 65 years) with leg ulcers were patch tested (Finn chambers) with Pyrogallol. Patch tests were evaluated according to the procedure of Wilkinson et al.[70] The distribution of leg ulcers was as follows: varicose ulcers (12 patients), postphlebitic ulcers (6 patients), and both varicose and postphlebitic ulcers (7 patients). Patients who had lesions for less than 12 months were excluded. Positive reactions to Pyrogallol were observed in 3 patients.[71]

A total of 8230 patients with allergic contact dermatitis were patch tested with cosmetic ingredients over a period of 15 years (1968–1983). Patch tests were conducted according to the method of Fregert et al.[72] Positive reactions to Pyrogallol (1% in petrolatum) were not reported.[73]

SUMMARY

Pyrogallol, a benzenetriol, is used in 82 hair dyes and colors at concentrations ranging from ≤ 0.1 to 5.0%. Typical use concentrations of Pyrogallol in oxidative hair dyes range between 0.25 and 0.383% by weight.

Noncosmetics uses of Pyrogallol include: developer in photography, mordant for wool, and the dying of furs.

Following the intraperitoneal injection of Pyrogallol (60 mg/kg) into female mice, the maximum concentration in the brain (28.4 μg/wet weight) was found at 10 min. At 15 min postinjection, the concentration of Pyrogallol approached zero.

Pyrogallol and resorcinol were detected (via TLC) in hydrolyzed urine extracts from adult albino rats 24 h after intraperitoneal injection (100 mg of Pyrogallol/kg) but were not detected in nonhydrolyzed urine extracts. Resorcinol was detected also in rat fecal extracts that had been incubated with Pyrogallol.

The oral LD_{50}'s for male and female rats dosed with technical synthetic Pyrogallol were 1270 mg/kg and 800 mg/kg, respectively. Oral LD_{50}'s for male and female rats dosed with technical natural Pyrogallol were 1270 mg/kg and 848 mg/kg, respectively. In another study, the oral LD_{50} of a 50% solution of Pyrogallol in DMSO was 1800 mg/kg (male rats).

Twenty-four hour applications of technical synthetic Pyrogallol and technical natural Pyrogallol in distilled water (doses = 2100 mg/kg) to the backs of Sprague-Dawley rats did not result in 50% mortality.

A hair dye containing 0.4% Pyrogallol did not induce gross or microscopic changes, except for slight thickening of the skin, in New Zealand white rabbits when applied (in hydrogen peroxide) to the skin twice weekly for 13 weeks.

In a study involving male New Zealand white rabbits, Pyrogallol (powder form) induced ocular irritation. Pyrogallol was not an ocular irritant when tested at a concentration of 1% in propylene glycol.

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A 50% reduction in viability was noted in B lymphocyte cultures treated with Pyrogallol (5 μg/culture). Pyrogallol (in ethanol or DMSO) did not cause plasma membrane damage when added to cultures of lung fibroblasts from human embryos.

Both technical synthetic and technical natural Pyrogallol (in distilled water) were slightly irritating to the skin of Dunkin Hartley guinea pigs. Pyrogallol (unrefined) also induced sensitization reactions when applied to the skin of guinea pigs.

Significant teratogenic effects were not observed in the offspring of female Sprague-Dawley rats dosed (via gavage) with Pyrogallol (in propylene glycol) on days 6 to 15 of gestation. The same was true for Charles River CD rats dosed (dermal applications) with a hair dye containing 0.4% Pyrogallol on days 1 to 19 of gestation. No treatment-related effects were observed in a multigeneration reproductive toxicity study in which Charles River CD rats received dermal applications of a hair dye that contained 0.4% Pyrogallol. The dye was mixed with an equal volume of 6% H_2O_2 before application.

In the Ames test, Pyrogallol was mutagenic to TA98, TA100, and TA1537 tester strains of *Salmonella typhimurium*. Technical synthetic Pyrogallol was mutagenic to L5178Y mouse lymphoma cells (*in vitro*) with and without metabolic activation. Technical synthetic Pyrogallol also induced chromosomal aberrations in human lymphocytes (*in vitro*) with and without metabolic activation.

Pyrogallol induced chromatid breaks and exchanges in cultures of Chinese hamster ovary cells with and without metabolic activation. Pyrogallol (at pH 10) was also mutagenic to strain D7 of *Saccharomyces cerevisiae* (*in vitro*) in the mitotic gene conversion assay. However, significant mutagenic activity was not noted at pH 7.

Pyrogallol (in 5% saccharose) was mutagenic to Berlin K and Basc strains of *Drosophila melanogaster* in the recessive lethal mutations test (*in vivo*). In the micronucleus test (*in vivo*), Pyrogallol significantly increased the percentage of micronucleated polychromatic erythrocytes in mouse bone marrow smears over that of controls. Pyrogallol also induced chromatid breaks in mouse bone marrow cells (*in vivo*).

In two carcinogenicity studies, the number of neoplasms in mice treated (dermal applications) with 50% Pyrogallol in acetone was not significantly different from that of controls. Similar results were reported in a carcinogenicity study in which a hair dye containing 0.49% Pyrogallol and H_2O_2 in aqueous solution was applied to the skins of mice. In another study, histiocytomas was noted at the exposure sites of 4 of 19 Fischer rats injected subcutaneously with Pyrogallol (in 50% DMSO). On the skin of female ICR/HA mice, Pyrogallol was reported to be an active cocarcinogen when applied with benzo[a]pyrene.

Sensitization reactions were noted in 3 of 25 patients (with leg ulcers) patch tested with Pyrogallol. In another sensitization study, 8230 patients with allergic contact dermatitis were patch tested with cosmetic ingredients over a period of 15 years. Positive reactions to Pyrogallol (1% in petrolatum) were not reported.

DISCUSSION

In animals, Pyrogallol was not a skin irritant. Positive and negative results were reported in two animal skin sensitization studies. The results of provocative patch tests involving contact dermatitis patients were negative. Hair dyes containing Pyrogallol are exempt from the principal adulteration provision and from the color additive provisions

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in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act of 1938 when cautionary statements and patch test instructions are conspicuously displayed on the label. Therefore, additional predictive human skin irritation and sensitization studies were not requested.

The Expert Panel noted that Pyrogallol was mutagenic in three tester strains of *Salmonella typhimurium* but also recognizes that the compound was negative for carcinogenicity in three chronic skin painting studies.

CONCLUSION

On the basis of the available animal and clinical data presented in this report, the CIR Expert Panel concludes that Pyrogallol is safe as a cosmetic ingredient in the present practices of use and concentration.

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June 5, 2007

Memorandum

To: CIR Expert Panel

From: Wilbur Johnson, Jr.
Senior Scientific Analyst

Subject: Pyrogallol

In 1991, CIR published a Final Report with the following conclusion: On the basis of the available animal and clinical data presented in this report, the CIR Expert Panel concludes that Pyrogallol is safe as a cosmetic ingredient in the present practices of use and concentration. A copy of this Final Report is included. Additionally, a search of the currently available scientific literature on Pyrogallol was performed, and the resulting data are summarized in the attached re-review background document. It is important to note that a 2-year dermal carcinogenicity study sanctioned by the National Toxicology Program was completed this year and that a draft report will be developed for peer review.

Pyrogallol was reported as being used in 42 hair dyes and colors (at concentrations of $\leq$0.1 % to 5%) in 1989. Data provided by FDA in 2006 indicated that Pyrogallol was being used in 11 hair dyes and colors. The results of an industry survey indicate that Pyrogallol is not being used in cosmetics, and, thus, the absence of use concentration data.

The task for the Panel at this meeting is to determine whether the conclusion on Pyrogallol is still valid. If it is not, an amendment should be initiated. If the conclusion is still valid, then the Panel should decide if there is a need for an addendum to add significant new safety or other data. If there is no such need, the Panel may simply describe the new information considered, reaffirm the original conclusion, and decide to not reopen.

RE-REVIEW DOCUMENT ON PYROGALLOL

In the *International Cosmetic Ingredient Dictionary and Handbook* **(Gottschalck and McEwen, 2006),** Pyrogallol is is defined as a phenol. The CIR Expert Panel has evaluated the safety of Pyrogallol in cosmetics, and a Final Report with the following conclusion was published in 1986: On the basis of the available animal and clinical data presented in this report, the CIR Expert Panel concludes that Pyrogallol is safe as a cosmetic ingredient in the present practices of use and concentration **(Elder, 1991)**

An updated search of the literature was performed to identify studies on Pyrogallol that have been published since the Panel's Final Safety Assessment was issued or were omitted from that report. These studies are summarized in this re-review document.

CHEMISTRY

DEFINITION

Pyrogallol

According to **Gottschalck and McEwen (2006)**, Pyrogallol (CAS No. 87-66-1) is a phenol with three OH substituents on the benzene ring. Technical/other names for this chemical include: Benzene-1,2,3-Triol, 2,3-Dihydroxyphenol, and 1,2,3-Trihydroxybenzene **(Gottschalck and McEwen, 2006)**.

CHEMICAL AND PHYSICAL PROPERTIES

Poitrast and Keller (1988) reported a log K_{ow} of 0.26 for 1,2,3-Trihydroxybenzene (Pyrogallol).

According to **Marklund and Marklund (1994)**, Pyrogallol is a potent generator of superoxide anion (O_2^-) and also generates hydroxyl radical (OH•) and hydrogen peroxide by the Haber-Weiss reaction ($O_2^- \pm H_2O_2/OH\bullet \pm O_2^- \pm O_2$).

Sottofattori et al. (1998) studied the effect of benzenediols and benzenetriols on the nitrosation of propranolol. The nitrosation of propranolol under the standard conditions recommended by the World Health Organization (10 mM propranolol hydrochloride, 40 mM sodium nitrite, PH 3.5) was carried out in the absence and in the presence of phenol, benzenediols, and benzenetriols added to the nitrosation mixture at concentrations ranging from 2 mM to 40 mM. The yield of N-nitrosopropranolol (NOP) was reduced, with potency decreasing in the following order: 1,2-benzenetriol > 1,2,3-benzenetriol (Pyrogallol)

> 1,4-benzenediol; the inhibitory effect was dose-dependent. The yield of NOP was increased by 1,3-benzenediol and 1,3,5-benzenetriol, but this effect was inversely related to the concentration.

USE

PURPOSE IN COSMETICS

Pyrogallol functions as a fragrance ingredient and hair colorant **(Gottschalck and McEwen, 2006)**.

SCOPE AND EXTENT OF USE IN COSMETICS

Frequency of use data provided by **FDA in 2006** indicated the use of Pyrogallol in 11 cosmetic products **(FDA, 2006)**. Previously, product formulation data submitted to FDA in 1989 indicated that Pyrogallol was being used in 42 hair dyes and colors at concentrations up to 5% **(Elder, 1986)**. These data are included in Table 1. No uses/use concentrations of Pyrogallol were reported in a cosmetics industry survey **(CTFA, 2007)**.

Table 1. Historical and current cosmetic product uses and concentrations for Pyrogallol

Product Category (FDA 2006)	1989 uses (Elder 1991)	Total products in category (Elder 1991)	2006 uses (FDA 2006)	Total products in category (FDA 2006)	1989 concentrations (Elder 1990) (%)	2007 concentrations (CTFA 2006) (%)
Hair coloring products	42	1164	11	1600	≤0.1 to 5	-*
Total uses/ranges for Pyrogallol	42		11		≤0.1 to 5	-

*In industry survey, no use concentrations reported for this category.

In the EEC (formerly the European Economic Community; currently known as the European Union) Cosmetics Directive (Annex II), Pyrogallol appears on the list of substances that must not form part of the composition of cosmetic products **(European Commission, 2007)**.

For cosmetic products marketed in Japan, Pyrogallol is included on the list of ingredients that cosmetics shall not contain. However, it is listed as an ingredient of quasi drug products designated for use directly on the body. Quasi drugs, by definition, must have a mild effect on the body, but are neither intended for the diagnosis, prevention, or treatment of disease, nor to affect the structure or function of the body **(Ministry of Health, Labor, and Welfare, 2001)**.

NONCOSMETIC USE

According to **21 CFR 73.1375**, the Food and Drug Administration classified Pyrogallol as exempt from certification as a color additive. Additionally, Pyrogallol may be safely used in combination with ferric ammonium citrate for coloring plain and chromic catgut sutures for use in general and ophthalmic surgery **(21 CFR 73.1375)**.

BIOLOGICAL PROPERTIES

METABOLISM

Miyazaki et al. (2004) investigated the oxidoreductive reactions of human hemoglobin with Pyrogallol, and the metabolism of Pyrogallol by the protein , which contains a protoporphyrin IX-like cytochrome P-450. Pyrogallol, having three hydroxy groups, oxidized human oxyhemoglobin to methemoglobin and reduced human methemoglobin to oxyhemoglobin. Since superoxide dismutase and catalase inhibited these reactions extensively, active oxygens such as superoxide and hydrogen peroxide were considered to be involved in the oxido-reductive reaction of human hemoglobin by Pyrogallol. It was also found that the metabolism of Pyrogallol to purpurogallin occurred quickly in human erythrocytes, i.e., when Pyrogallol was added to human erythrocyte suspensions, it oxidized intracellular hemoglobin and produced purpurogallin. The metabolism of Pyrogallol to purpurogallin was explained by the Pyrogallol oxidation with the superoxide and hydrogen peroxide that was produced during the oxidoreductive reactions of human hemoglobin with Pyrogallol.

EFFECT ON MUSCLE CONTRACTION

Goldschmidt and Tallarida (1991) studied the effect of Pyrogallol on muscle contraction (endothelium-intact aortic rings) in an isolated muscle bath preparation. In preconstricted rings with an intact endothelium, Pyrogallol (1 µM) produced a rapid increase in contractile tension that reached a stable level within one minute. In aortic rings denuded of endothelium, Pyrogallol had no effect.

EFFECT ON PROTEIN SYNTHESIS

Adcock et al. (1994) examined the effect of Pyrogallol, an O_2- generator, on the ability of human epithelial cells to produce active DNA binding proteins and inducible nitric oxide synthase (iNOS) mRNA in cultured type II airway epithelial cells (A549 cells). Cells were incubated with a range of concentrations of Pyrogallol (10^{-7} to 10^{-4} M) for various time periods of up to two hours. NfkB binding in the nuclei of these

cells was determined by electrophoretic mobility shift assays. iNOS mRNA was measured using reverse transcription and the polymerase chain reaction (PCR) method. There was a time- and concentration-dependent induction of Nf*k*B binding, followed by a time- and dose-dependent increase in iNOS mRNA levels. These results suggest that, in the airways, the initial response to oxidative stress may be to induce Nf*k*B-responsive genes, such as iNOS, which may play an important role in defending the airway against oxidative stress.

EFFECT ON RESPIRATION

In a study by **Szabó et al. (1996)**, the exposure of J774 cells (mouse macrophage cell line) to Pyrogallol (100 µM) for 24 hours produced a statistically significant ($p < 0.01$, compared to control) decrease in mitochondrial respiration.

TOXICOLOGY

SUBCHRONIC DERMAL TOXICITY

Batelle Labs (2004) conducted a subchronic dermal toxicity study on Pyrogallol using groups of twenty F344 rats (10 males, 10 females per group). This study is actually the dose range-finding study for NTP's 2-year dermal carcinogenicity study on Pyrogallol. A status report on this study is included in the section on Carcinogenicity later in the report text. Pyrogallol was administered (in 95% ethanol) dermally at dosages of 0, 9.5, 18.75, 37.5, 75, and 150 mg/kg for up to 14 weeks (weekdays only). Treatment-related clinical signs were brown staining and irritation at the site of application. There was one early death (0 mg/kg female) that was unrelated to dosing with Pyrogallol. There were no treatment-related body weight effects in this study. In addition, no treatment-related hematology or clinical chemistry changes were noted. Treatment-related histopathologic findings were reported only at the site of application (epidermal hyperkeratosis, epidermal squamous hyperplasia, and chronic-active inflammation of the dermis), generally with an increase in incidence and severity, corresponding to increasing dosages throughout all of the dosages administered (except for the 9.5 mg/kg female). Based on the results of this study, it was recommended that dosages of 150, 75, and 37.5 mg/kg be considered for the chronic study using male and female F344 rats.

CYTOTOXICITY

Koo et al. (2004) studied the role of superoxide anion ($O2^{\cdot-}$) in neuronal cell injury induced by reactive oxygen species (ROS) in PC12 cells using Pyrogallol as a donor to release $O2^{\cdot-}$. Cell death was assessed by the measurement of released lactate dehydrogenase (LDH) into the culture medium. Pyrogallol at concentrations greater than 0.2 mM caused a time-dependent cell death. After exposure to 0.5 mM Pyrogallol, the released LDH rapidly increased up to approximately 72% at 5 hours. Mild cell death was observed at 0.2 mM Pyrogallol, when approximately 56% of the LDH was released at 24 hours. However, at 0.1 mM Pyrogallol, the released LDH level was comparable to that of control cells.

HEPATOTOXICITY

Gupta et al. (2002) studied the hepatotoxicity of Pyrogallol using groups of 8 adult Wistar albino rats (4 males, 4 females/group; weights = between 200 and 250 g). Pyrogallol was injected intraperitoneally at a dose of 100 mg/kg. At 1 hour after dosing, blood was drawn by cardiac puncture for the estimation of serum markers (aminotransaminase [AST], alanine aminotransaminase [ALT], and alkaline phosphatase). The rats were later killed and livers were removed and processed for MDA and GSH and tissue histology. Pyrogallol (dose = 100 mg/kg) produced significant liver damage, as indicated by a marked increase in serum AST and ALT, compared to the control group ($p < 0.05$). The serum AST and ALT increased to 357.0 ± 30.7 IU/l and 147.8 ± 28.4 IU/l, respectively, compared to 208.4 ± 4.1 IU/l and 84.5 ± 19.5 IU/l, respectively, in control animals. However, there was an insignificant change in the levels of alkaline phosphatase in the Pyrogallol-treated group; values for Pyrogallol-treated animals and the control group were 216.6 ± 44.1 IU/l and 240 ± 16.3 IU/l, respectively.

Pyrogallol (dose = 100 mg/kg) produced significant oxidative stress in liver tissue, as indicated by the marked increase in malondialdehyde (MDA) and glutathione (GSH) levels (markers of oxidative stress), compared to the control group. The MDA levels increased significantly to 311 ± 18.29 nmol/g wet tissue, compared to 170 ± 16.8 nmol/g wet tissue, respectively ($p < 0.05$). Glutathione levels also increased significantly to 37 ± 2.25 µg/g wet tissue, compared to a control value of 24.4 ± 3.6 µg/g wet tissue ($p < 0.05$).

The Pyrogallol-treated rats had mild inflammatory changes in the liver. The changes included

cellular infiltration of leukocytes and sinusoidal dilation, even as early as 1 hour after Pyrogallol administration **(Gupta et al. 2002)**.

ANTITHYROID ACTIVITY

Lindsay et al. (1992) evaluated the antithyroid activity of Pyrogallol. Porcine thyroid peroxidase (TPO)-catalyzed iodination of bovine serum albumin was assayed. The concentration at which 50% inhibition of porcine thyroid peroxidase activity (ID50) occurred was determined. The mean ID50 for Pyrogallol (based on 5 experiments) was 3.8 ± 0.12 nmol/ml). The known TPO inhibitor and antithyroid drug 6-N-propyl-2-thiouracil (PTU) served as the reference standard. The mean ID50 for PTU was 7.2 ± 0.16 nmol/ml.

INDUCTION OF HYPERPLASIA

In a study by **Hirose et al. (1986),** Pyrogallol (1% in the diet) was fed by continuous oral administration to groups of 15 male Syrian golden hamsters for 20 weeks. The control group (15 hamsters) was fed basal diet. Mild hyperplasia of the forestomach was noted in 15 hamsters ($p < 0.001$, compared to control group). Four hamsters had moderate hyperplasia of the forestomach. Oral dosing induced neither severe hyperplasia nor papillomas. Seven hamsters fed basal diet only had mild hyperplasia of the forestomach, and 1 hamster fed basal diet only had moderate hyperplasia of the forestomach.

EFFECT ON GENE EXPRESSION

Choi and Moore (1993) studied the induction of c-fos and c-jun gene expression by phenolic antioxidants. Following the treatment of quiescent human hepatoma HepG2 cells with Pyrogallol (200 µM) , the levels of c-fos and c-jun mRNAs were substantially increased. Phenolic antioxidants specifically induce expression of the c-fos and c-jun mRNAs. The antioxidant-specific induction of c-fos/CAT (chloramphenicol acetyltransferase) promoter constructs in transient transfections indicates that at least a portion of this response is transcriptional.

GENOTOXICITY/MUTAGENICITY

Sakagami et al. (1986) conducted a study to evaluate the mutagenicity of Pyrogallol, using the Ames test and the liquid rec assay. The Ames test was performed with *Salmonella typhimurium* strains TA98 and TA100, and the liquid rec-assay (for DNA damage) was performed with *Bacillus subtilis* strains

H-17 (Rec^+) and M-45 (Rec^-). Both assays were conducted with metabolic activation. Pyrogallol was tested at a dose of 125 µg/ml in strains TA98 and TA100 (Ames test). In the rec assay , Pyrogallol was tested at doses of 375 µg/ml (strain M-45) and 500 µg/ml. Results for Pyrogallol were positive in both assays.

Sakagami et al. (1988) evaluated the genotoxicity of Pyrogallol in the *umu* test, with and without metabolic activation. This genotoxicity assay is based on the ability of toxic chemicals to induce *umu* gene expression in *Salmonella typhimurium* TA1535/pSWK 1002 in which a plasmid pSK 1002 carrying a fused gene *umu*C' - '*lac*Z has been introduced. Pyrogallol was tested at concentrations up to 3200 µg/ml, and results were positive without, but not with, metabolic activation.

Kawanishi et al. (1989) studied the reactivity of Pyrogallol with DNA using a DNA sequencing technique that involved ^{32}P 5'-end-labeled DNA fragments that were obtained from human c-Ha-ras-1 protooncogene. The reaction mixture contained ^{32}P-labeled 351 base pair DNA fragment and 5 mM of benzene or Pyrogallol in 200 µl of 20 mM Tris-HCl buffer at pH 8.0. The mixture was incubated for 30 or 90 minutes. Little or no cleavage was observed with Pyrogallol, even with alkali treatment.

Glatt et al. (1989) evaluated the genotoxicity of Pyrogallol in the micronucleus test (Chinese hamster V79 cells) and in the sister chromatid exchanges assay (Chinese hamster V79 cells). In the micronucleus test, an elevated frequency of micronucleated cells was noted. At the optimal/maximal concentration of 50 µM Pyrogallol, the frequency of micronucleated cells x 10^3 above background was 32. It was noted that higher test concentrations were used; however, the frequency of the micronucleated cells declined towards the value of the solvent controls. In control cultures, the frequency of micronucleated cells was usually approximately 10 x 10^{-3}.

In the sister chromatid exchanges assay, at the optimal/maximal concentration of 25 µM Pyrogallol, the mean number of SCEs per cell above background was 3.2. This value was statistically significant ($p > 0.05$). The number of SCEs (mean ± standard deviation) in control cultures varied from 6.2 ± 2.9 to 8.4 ± 2.6 Pyrogallol induced sister chromatid exchanges **(Glatt et al.1989)**.

Watanabe et al. (1991) evaluated the mutagenicity of Pyrogallol using *Salmonella typhimurium* strain TA98 both with and without metabolic activation. Pyrogallol was tested at doses up to 30 µg/plate, and was not mutagenic either with or without metabolic activation.

Lin and Lee (1992) evaluated the mutagenicity of Pyrogallol in the Ames *Salmonella* mutagenicity test using *Salmonella typhimurium* strains TA97, TA98, and TA100. Pyrogallol was tested at does up to 500 µg/plate both with and without metabolic activation. Pyrogallol was highly mutagenic to strains TA97 and TA100. Mutagenicity was reduced slightly by the treatment of Pyrogallol with chlorine or nitrite.

Lee and Lin (1994) studied the mutagenicity of Pyrogallol (in DMSO; test concentration = 56 µg/plate) using the Ames test with and without metabolic activation. *Salmonella typhimurium* strains TA97, TA98, and TA100 were used. Pyrogallol was highly mutagenic to strain TA100 without, but not with, metabolic activation.

Watanabe et al. (1998) evaluated the mutagenicity of Pyrogallol in the plate incorporation assay (testing at two laboratories) using the following bacterial strains without metabolic activation: *Salmonella typhimurium* strains TA102 and TA2638 and *Escherichia coli strains* WP2/pkM101 and WP2 *uvr*A/pKM101. Because of toxicity induced in the strains tested, the highest concentration at which it was possible to conduct tests involving all of the strains was 625 µg/plate. Pyrogallol was mutagenic to all of the bacterial strains that were tested; results were positive at both laboratories.

Silva et al. (2003) studied the induction of chromosomal aberrations by Pyrogallol in V79 cells at different pH values (6.0, 7.4, and 8.0). Pyrogallol caused a clear clastogenic effect in a pH-dependent way. At pH 6.0, Pyrogallol at higher doses (60 and 80 µM) significantly increased the level of chromosomal aberrations in V79 cells. However, at pH values of 7.4 and 8.0, Pyrogallol also induced significant levels of chromosomal aberrations at lower doses (< 80 µM). Pyrogallol at higher doses, and in a pH-dependent manner, caused a significant induction of multi-aberrant cells (cells with more than 10 chromosomal aberrations). The authors noted that the results of this study (all experiments) suggest that the genotoxicity of Pyrogallol is almost exclusively mediated by reactive oxygen species.

In a micronucleus test **(National Toxicology Program [NTP] 2004)**, groups of B6C3F1 mice (5 males, 5 females/group) were dosed dermally with Pyrogallol (in 0.2% Methylcellulose) over a period of 90 days. The groups received doses of 0, 38, 75, 150, 300, and 600 mg/kg, respectively. Blood samples were collected at 24 hours. Results were equivocal for male mice and negative for female mice.

Mazzei et al. (2006) investigated the possible mutagenicity of three commercial Pyrogallol-

containing (concentration of Pyrogallol not stated) hair gels made in Brazil (pH range: 3.5 to 4.0) using the *Salmonella* mutagenicity assay and the mouse bone marrow micronucleus assay. In the *Salmonella* mutagenicity assay using 648 to 5000 µg/plate of cosmetic samples, none of the samples reached a 2-fold increase in revertants relative to controls. Both with and without metabolic activation, the dose-response relation in strains TA98, TA100, TA102, TA1535, and TA1537 was not significant ($p > 0.01$).

In the mouse bone marrow micronucleus assay, 10 Swiss male mice were dosed orally with 2000 mg/kg of sample per body weight/day. The animals were killed at 48 hours after administration of the first dose. Bone marrow was extracted from the femur and slides prepared. The ratio between polychromatic and normochromatic erythrocytes as well as the presence of micronuclei in bone marrow cells were determined. Equal numbers of micronucleated polychromatic erythrocytes were detected between the cells of each treated group and the negative control using ANOVA and χ-square analyses. Thus, none of the products induced mutagenesis in either assay **(Mazzei et al. 2006)**.

CARCINOGENICITY

According to the **National Toxicology Program (NTP) (2007)**, the 2-year dermal carcinogenicity study on Pyrogallol has been completed and the histopathology review is ongoing. NTP projects that a draft report will be issued in approximately five months. The results of the dose range-finding study that was conducted prior to initiation of this 2-year dermal carcinogenicity are summarized in the section on Subchronic Dermal Toxicity earlier in the report text.

TUMOR PROMOTION

Bohrman et al. (1988) reported the results of an interlaboratory study to evaluate the usefulness of the Chinese hamster V79 cell metabolic cooperation assay to predict the tumor-promoting activity of selected chemicals. The biological basis for this assay is the inhibition of gap-junctional communication by test chemicals. Results were positive for Pyrogallol (test concentration range: 0.25 to 3.0 µg/ml) at one laboratory and negative at the other; overall, the results for Pyrogallol were classified as equivocal. Chemicals were scored as positive (at least two concentration levels statistically different from the control), equivocal (only one concentration statistically different), or negative. An overall evaluation of the V79 system for predicting in vivo promotion activity was said to be difficult because of the organ specificity of

certain chemicals and/or the limited number of adequately tested nonpromoting chemicals.

ANTITUMOR ACTIVITY

Khan et al. (2002) studied the antiproliferative activity of Pyrogallol on human tumor cell lines. The effects of this chemical on in vitro cell growth were presented; the inhibition of tumor cell proliferation was consistently observed. The IC50 of Pyrogallol on K562, Jurkat, HEL, and Raji cell lines was found to be in the range of 10 to 30 μM.

EFFECT ON ATPASE ACTIVITY AND ANTIGEN EXPRESSION

Gruner et al. (1992) studied the effect of Pyrogallol on ATPase activity and Ia antigen expression on murine epdermal Langerhans cells. Balb/c mice (8 mice per group) were smeared with ointments containing different concentrations of Pyrogallol and tested 3 days later for ATPase and IA positive Langerhans cells. A statistically significant reduction of ATPase positive Langerhans cells was observed at Pyrogallol concentrations of 5% or higher ($p < 0.05$).

SKIN SENSITIZATION

In a study conducted by **White and Guo (2006)**, the objective was to determine the potential for Pyrogallol to elicit an allergic response when applied dermally to groups of 6 female BALB/c mice (hepatitis and Sendai virus free). Measurement of the contact hypersensitivity response was initially accomplished using the local lymph node assay (LLNA). In the first LLNA, the mice were sensitized to 2.5%, 5%, 10%, 25%, and 50% Pyrogallol. Since Pyrogallol , at all five concentrations, produced a significant increase in the proliferatiion of lymph node cells, two additional LLNAs were performed. The concentrations of Pyrogallol in the second study were 0.5%, 1.0%, and 2.5%. In the third study, Pyrogallol was tested at concentrations of 0.25%, 0.5%, 1.0%, 2.5%, 5%, and 10%.

Based on the results of the LLNA, a primary irritancy assay study was conducted using exposure levels of 0.125%, 0.25%, 1.0%, 5%, and 10%. Data from the irritancy study showed that Pyrogallol was an irritant at a concentration as low as 0.125%. As noted in the LLNA, a positive response was observed at a concentration of 0.5% Pyrogallol. Thus, it seemed that the significantly increased proliferation observed in the LLNA might have been due to the irritant effect of Pyrogallol.

To further determine if Pyrogallol was primarily an irritant, two mouse ear swelling tests (MEST) were performed. In the first MEST, mice were sensitized with Pyrogallol at concentrations of 0.25%, 1%, and 5%, and challenged with 0.25% Pyrogallol. There was no significant difference when the naive, vehicle, and three dose groups were compared to background control at either the 24- or 48-hour time point. In the second MEST, mice were sensitized with Pyrogallol at concentrations of 1% and 5%, and challenged with 1% Pyrogallol. A significant increase in mouse ear thickness was observed at 66 hours after challenge in mice that were sensitized with 5% Pyrogallol. 1-fluoro-2,4-dinitrobenzene (2,4-dinitrofluorobenzene, DNFB) was used as the positive control at a concentration of 0.15% for the irritancy test, LLNA, and MEST.

Taken together, these results demonstrate that Pyrogallol is a weak sensitizer, but a strong irritant in female BALB/c mice. The positive response observed in the LLNAs is mainly due to the irritant effect of Pyrogallol **(White and Guo 2006)**.

EFFECT ON CONTACT SENSITIZATION

Gruner et al. (1992) conducted an experiment (12 Balb/c mice) to determine whether contact sensitization to DNFB is altered in skin sites treated with Pyrogallol. A shaved abdominal skin site on each animal was treated with an ointment containing Progallol on two consecutive days, before and after contact sensitization with 1-fluoro-2,4-dinitrobenzene (DNFB), to affect the induction phase of contact hypersensitivity (antigen presentation by Langerhans cell). At 5 days later, challenge with DNFB was performed on the ear skin; the swelling response at this site was measured two days later. No reduction of contact sensitization was observed after treatment with Pyrogallol (in ointment).

CLINICAL ASSESSMENT OF SAFETY

SKIN SENSITIZATION

Guerra et al. (1992a) reported the frequency of sensitization to hairdressing allergens in a group of patients with contact dermatitis. From 1985 to June of 1990, 261 hairdressers' clients (5 males, 256 females; mean age = 43.3 years) were examined. Patch tests were conducted and reactions were read ant 2 and 3 days. The rate of sensitization to Pyrogallol was 2.3%.

Guerra et al. (1992b) presented the results of a multicenter study that was performed in 9 Italian centers by members of the Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali (GIRDCA). The purpose of this study (from January 1985 to June 1990) was to evaluate the frequency and source of contact sensitization in a group of 302 hairdressers (mean age: 24.6 years) with dermatitis. Patch tests were performed according to International Contact Dermatitis Research Group (ICDRG) recommendations, using Finn chambers on Scanpor tape. The reactions were read at 2 and 3 days. A low incidence of sensitization (1.3%) was reported for Pyrogallol (1% in petrolatum).

Frosch et al. (1993) presented patch test results for 809 hairdressers tested at a total of nine European Centers. With the exception of three centers, the majority of the patients were seen during the years 1988 to 1991. Most of the patients were hairdressers with hand eczema. Reactions were classified as allergic reactions based on their morphology and time course, according to the generally accepted criteria of the International Contact Dermatitis Research Group. Doubtful or irritant reactions were excluded. The sensitization frequency for Pyrogallol (1% in petrolatum) in hairdressers was 0.8%.

Leino et al. (1998) patch tested (Finn chambers) 54 hairdressers with suspected occupational eczema. The tests were scored when patches were removed (at 48 hours), and, also at 24 and 48 to 120 hours later. The tests were scored according to the recommendations of the International Contact Dermatitis Research Group. Cutaneous reactions that were scored as 1+, 2+, and 3+ were considered allergic. None of the 54 hairdressers had a positive reaction to Pyrogallol.

Goossens et al. (1999) reported the results of a retrospective European survey of allergic contact reactions to cosmetics. Data on 475 patients with contact allergy to cosmetic ingredients, observed during a 4-month period (January-April 1996), were collected in 5 European dermatology centers. One reaction to Pyrogallol (from center in Belgium) was reported.

Barbaud et al. (2001) evaluated the skin sensitization potential of Pyrogallol using 19 patients in a standard patch test conducted according to the European Contact Dermatitis Research Group patch test procedure. Pyrogallol was tested at a concentration of 1% in vaseline. Positive reactions were observed in nine of the 19 patients tested.

Hillen et al. (2007) patch tested 1320 patients (1030 females, 290 males) because of suspected

allergic contact dermatitis of the scalp. The patients were patch tested between 1993 and 2003. Of the 1320 patients, 628 were patch tested with 1% Pyrogallol according o the criteria of the International Contact Dermatitis Research Group. Of the 628 patients, 5.4% had positive reactions to 1% Pyrogallol.

EPIDEMIOLOGY

The CIR Expert Panel concluded that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other endpoints. A discussion of the available hair dye epidemiology data is available at http://www.cir-safety.org/findings.shtml. **

The Expert Panel recognizes that Pyrogallol is used as a hair dye ingredient and may be a sensitizer. However, hair dyes containing these ingredients, as coal tar hair dye products are exempt from the principal adulteration provision and from the color additive provisions in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act, when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Expert Panel expects that continuing to follow this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures.

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