Amended Safety Assessment of Pyrogallol as Used in Cosmetics

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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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555 13th Street, NW, Suite 300W, Washington, DC 20004
cirinfo@cir-safety.org

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 hair dye 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]

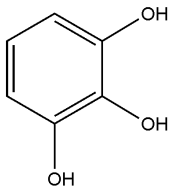


Figure 1. Pyrogallol

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 points of reference, in 1989, the maximum concentration of use range was reported to be < 0.1 - 5% in hair dyes and colors,[2] but no concentrations of use were reported in a survey conducted for the 2007 re-review.[3]

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.[11,12] 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 an approved color additive 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.[13]

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.[14] 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.[15] 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.[16] 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.[16]

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).[3,16-20] In a chromosomal aberration test with 20, 40, 60, and 80 µM Pyrogallol, significant increases in the percentage of aberrant cells were observed with 60 µM at pH 8.0 and with 80 µM at pH 6.0 and 7.4, with greater responses generally observed at pH 7.4 and 8.0 than at pH 6.0; however, at pH 8.0, 80 µM was cytotoxic, and chromosomal aberration results were not reported.[21] 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.[22] 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.[16,19]

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.[16] 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.[16]

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.[16]

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.[16]

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.[23] 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.[24] 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.[25] 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.[26] 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).[27] 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.[28] 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.[29] 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.[30] 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.[31] 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.[32] 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.[33] 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.[34] 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.[35] 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.[36] 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.[37] 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.[31] 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.[38] 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..[39-41] 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).[40,41] 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.[39] 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.[42] 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.[43] 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.[43] 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).[33]

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%.[44-47] In a retrospective study of sensitization to resorcinol, the sensitization rate to 1% Pyrogallol was 47% (9 out of 19 patients).[48] 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.[47]

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).[49-51]

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 points of reference, in 1989, the maximum concentration of use range was reported to be < 0.1 - 5% in hair dyes and colors, but no concentrations

of use were reported in a survey conducted for the 2007 re-review. 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

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 Federal 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. Thus, determination of safety for Pyrogallol outside of use for hair dyes is not within the purview of the Panel. 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 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.

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 hair dye 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	[19]
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	[16]
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	[17]
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	[20]
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	[18]
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	[16]
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	Statistical significance was not indicated for the responses at 20, 40, or 60 µM at pH 6.0 and 7.4, or at 20 or 40 µM at pH 8.0. Significant increases in the percentage of aberrant cells at 60 µM at pH 8.0 and at 80 µM at pH 6.0 and 7.4. At pH 8.0, 80 µM was cytotoxic, and chromosomal aberration results were not reported. The researchers noted that results suggest the genotoxicity of Pyrogallol is almost exclusively mediated by ROS.	[21]
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	[22]
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)	[22]

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	[19]
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	[16]
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	[16]

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	[43]
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	[43]
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	[43]

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%	[44]
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	[45]
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	[48]
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%	[46]
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% ($p < 0.001$)	[47]

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	[49]
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	[50]
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	[51]

REFERENCES

1. Personal Care Products Council. 2026. *International Cosmetic Ingredient Dictionary*. https://incipedia.personalcarecouncil.org/winci/ . Date Accessed: January 24, 2026.
2. Elder RL. Final Report on the Safety Assessment of Pyrogallol. *J Am Coll Toxicol*. 1991;10(1):67–85.
3. Cosmetic Ingredient Review Expert Panel. 2007. Re-Review on Pyrogallol. Washington, D.C. [Unpublished re-review for Pyrogallol presented at the June 4-5, 2007 CIR Expert Panel meeting].
4. European Chemicals Agency. 2019. Pyrogallol CAS No. 87-66-1. https://echa.europa.eu/registration-dossier/-/registered-dossier/25683/7/3/4. Date Accessed: October 22, 2024.
5. National Center for Biotechnology Information. 2024. PubChem Compound Summary for CID 1057, Pyrogallol. https://pubchem.ncbi.nlm.nih.gov/compound/1057. Date Accessed: October 29, 2024.
6. Marklund S, Marklund G. Involvement of the superoxide anion radical in the autoxidation of pyrogallol and a convenient assay for superoxide dismutase. *Eur J Biochem*. 1974;47(3):469–474.
7. U.S. Food and Drug Administration. Federal Food, Drug, and Cosmetic Act Section 612 Title 21.
8. Hicks J., Eisenmann C., Nikitakis J., Kim D., Flores W. 2025. Personal Care Products Council RLD Mapping Project Report. Washington, DC [Analysis results provided as a courtesy to CIR].
9. U.S. Food and Drug Administration Office of Colors and Cosmetics (OCAC). 2025. Data from: Registration and Listing of Cosmetic Product Facilities and Products. College Park, MD [Obtained under the Freedom of Information Act].
10. Personal Care Products Council. 2025. Concentration of Use by FDA Product Category: Pyrogallol. [Unpublished data submitted by the Personal Care Products Council on March 27, 2025].
11. Goossens A. Self-testing for contact sensitization to hair dyes. *Contact Dermatitis*. 2012;66(6):299.
12. Thyssen JP, Sosted H, Uter W, Schnuch A, et al. Self-testing for contact sensitization to hair dyes - scientific considerations and clinical concerns of an industry-led screening programme. *Contact Dermatitis*. 2012;66(6):300–311.
13. EUR-Lex. 2009. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (recast). (Text with EEA relevance). https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02009R1223-20231201&qid=1704209440026. Date Accessed: October 25, 2024.
14. Kim Y, Kim H, Lee J, Im J, Kim K. Analytical method development and dermal absorption of pyrogallol, a hair dye ingredient. *Toxics*. 2022;10(10):570.
15. Miyazaki K, Arai S, Iwamoto T, Takasaki M, Tomoda A. Metabolism of pyrogallol to purpurogallin by human erythrocytic hemoglobin. *Tohoku J Exp Med*. 2004;203(4):319–330.
16. National Toxicology Program. 2013. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Pyrogallol (CAS No. 87-66-1) in F344/N Rats and B6C3F1/N Mice. NTP TR 574, NIH Publication No. 13-5916. https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr574_508.pdf. Date Accessed: October 23, 2024.
17. Takemura Y, Want DH, Sauriasari R, et al. Evaluation of pyrogallol-induced cytotoxicity in catalase-mutant Escherichia coli and mutagenicity in Salmonella typhimurium. *Bull Environ Contam Toxicol*. 2010;84(3):347–350.
18. Watanabe K, Sakamoto K, Sasaki T. Comparisons on chemically-induced mutation among four bacterial strains, Salmonella typhimurium TA102 and TA2638, and Escherichia coli WP2/pKM101 and WP2 uvrA/pKM101: Collaborative study II. *Mutat Res*. 1998;412(1):17–31.
19. Mazzei JL, da Silva DN, Oliveira V, et al. Absence of mutagenicity of acid pyrogallol-containing hair gels. *Food Chem Toxicol*. 2007;45(4):643–648.
20. Lee S, Lin J. Generation of hydrogen peroxide, superoxide anion and the hydroxyl free radical from polyphenols and active benzene metabolites: Their possible role in mutagenesis. *J Biomed Sci*. 1994;1(2):125–130.
21. do Ceu Silva M, Gaspar J, Silva ID, Leao D, Rueff J. Induction of chromosomal aberrations by phenolic compounds: Possible role of reactive oxygen species. *Mutat Res*. 2003;540(1):29–42.
22. Hossain MZ, Gilbert SF, Patel K, Ghosh S, Bhunia AK, Kern SE. Biological clues to potent DNA-damaging activities in food and flavoring. *Food Chem Toxicol*. 2013;55:557–567.
23. Mercado-Feliciano M, Herbert RA, Wyde ME, et al. Pyrogallol-associated dermal toxicity and carcinogenicity in F344/N rats and B6C3F1/N mice. *Cutan Ocul Toxicol*. 2013;32(3):234–240.

24. Hirose M, Inoue T, Asamoto M, Tagawa Y, Ito N. Comparison of the effects of 13 phenolic compounds in induction of proliferative lesions of the forestomach and increase in the labeling indices of the glandular stomach and urinary bladder epithelium of Syrian golden hamsters. *Carcinogenesis*. 1986;7(8):1285–1289.

25. Bohrman JS, Burg JR, Elmore E, et al. Interlaboratory studies with the Chinese hamster V79 cell metabolic cooperation assay to detect tumor-promoting agents. *Environ Mol Mutagen*. 1988;12(1):33–51.

26. Khan M, Lampronit I, Martello D, et al. Identification of pyrogallol as an antiproliferative compound present in extracts from the medicinal plant Emblica officinalis: Effects on in vitro cell growth of human tumor cell lines. *Int J Oncol*. 2002;21(1):187–192.

27. Zhou B, Wang L, Ren Z, et al. Pyrogallol promotes growth arrest by activating the p53-mediated up-regulation of p21 and p62/SQSTM1-dependent degradation of β-catenin in nonsmall cell lung cancer cells. . *Environ Toxicol*. 2023;39(4):2150–2165.

28. Shirani A, Mirabbasi R, Shabani L, et al. Pyrogallol acts as a novel anticancer factor to enhance the sensitivity to cisplatin in ovarian cancer cells through inducing miR-15a upregulation. *Egypt J Med Hum Genet*. 2025;26(1):15.

29. Ahn H, Im E, Lee DY , et al. Antitumor effect of pyrogallol via miR-134 mediated S-phase arrest and inhibition of PI3K/AKT/Skp2/cMyc signaling in hepatocellular carcinoma. *Int J Mol Sci*. 2019;20(16):3985.

30. Revathi S, Hakkim FL, Kumar NR, et al. In vivo anti-cancer potential of pyrogallol in murine model of colon cancer. . *Asian Pac J Cancer Prev*. 2019;20(9):2645–2651.

31. Venkatesan KB, Srinivasan MK, Prasad M, Jayaseelan N, et al. Pyrogallol induces apoptosis, oxidative stress and cell cycle arrest in C6 glioma cells: a potential therapeutic agent. *Med Oncol*. 2025;42(8):290.

32. Choi H, Moore DD. Induction of c-fos and c-jun gene expression by phenolic anitoxidants. *Mol Endocrinol*. 1993;7(12):1596–15602.

33. Gruner S, Zwirner A, Strunk D, Sonnichsen N. The influence of topical dermatological treatment modalities on epidermal Langerhans cells and contact sensitization in mice. *Contact Dermatitis*. 1992;26(4):241–247.

34. Koo B, Lee W, Chung K, Ko J, Kim C. A water extract of Curcuma longa L (Zingiberaceae) rescues PC12 cell death caused by pyrogallol or hypoxia/reoxygenation and attenuates hydrogen peroxide induced injury in PC12 cells. *Life Sci*. 2004;75(19):2363–2375.

35. Ahamad N, Anjum S, Ahmed S. Pyrogallol induces oxidative stress defects in the fission yeast S. pombe. *MicroPub Biol*. 2021;2021:10.

36. Lim JY, Kim C, Rhee JH, et al. Effects of pyrogallol on growth and cytotoxicity of wild-type and katG mutant strains of Vibrio vulnificus . *PLoS One*. 2016;11(12):e0167699.

37. Han YH, Park WH. Pyrogallol-induced As4.1 juxtaglomerular cell death is attenuated by MAPK inhibitors via preventing GSH depletion. *Arch Toxicol*. 2010;84(8):631–640.

38. Mendes V, Vilaca R, de Freitas V, et al. Effect of myricetin, pyrogallol, and phloroglucinol on yeast resistance to oxidative stress. *Oxid Med Cell Longev*. 2015;2015:782504.

39. Upadhyay G, Tiwari MN, Prakash O, et al. Involvement of multiple molecular events in pyrogallol-induced hepatotoxicity and silymarin-mediated protection: Evidence from gene expression profiles. *Fd Chem Toxicol*. 2010;48(6):1660–1670.

40. Upadhyay G, Singh AK, Kumar A, et al. Resveratrol modulates pyrogallol-induced changes in hepatic toxicity markers, xenobiotic metabolizing enzymes and oxidative stress. *Eur J Pharmacol*. 2008;596(1-3):146–152.

41. Upadhyay G, Kumar A, Singh MP. Effect of silymarin on pyrogallol- and rifampicin-induced hepatotoxicity in mouse. *Eur J Pharmacol*. 2007;565(1-3):190–201.

42. Gupta YK, Sharma M, Chaudhary G. Pyrogallol-induced hepatotoxicity in rats: A model to evaluate antioxidant hepatoprotective agents. *Methods Find Exp Clin Pharmacol*. 2002;24(8):497–500.

43. Guo TL, Germolec DR, Zhang LX, Auttachoat W, Smith MJ, White KL. Contact sensitizing potential of pyrogallol and 5-amino-o-cresol in female BALB/c mice. *Toxicology*. 2013;314(203):202–208.

44. Guerra L, Bardazzi F, Tosti A. Contact dermatitis in hairdressers' clients. *Contact Dermatitis*. 1992;26(2):108–111.

45. Goossens A, Beck MH, Haneke E, et al. Adverse cutaneous reactions to cosmetic allergens. *Contact Dermatitis*. 1999;40(2):112–113.

46. Hillen U, Grabbe S, Uter W. Patch test results in patients with scalp dermatitis: analysis of data of the Information Network of Departments of Dermatology. *Contact Dermatitis*. 2007;56(2):87–93.

47. Tsimpidakis A, Tsaoutou K, Nicolaidou E, et al. Patterns of sensitization and cross-reactivity in hair dye allergy: An 18-year tertiary-center experience from Greece. *Dermatitis*. 2026;online ahead of publication:17103568251408797.

48. Barbaud A, Reichert-Penetrat S, Trechot P, Granel F, Schmutz JL. Sensitization to resorcinol in a prescription verrucide preparation: Unusual systemic clinical features and prevalence . *Ann Dermatol Venereol*. 2001;128(5):615–618.

49. Leino T, Tammilehto L, Hytonen M, Sala E, Paakkulainen H, Kanerva L. Occupational skin and respiratory diseases among hairdressers. *Scand J Work Environ Health*. 1998;24(5):398–406.

50. Guerra L, Tosti A, Bardazzi F, et al. Contact dermatitis in hairdressers: The Italian experience. *Contact Dermatitis*. 1992;26(2):101–107.

51. Frosh PJ, Burrows D, Camarasa JG, et al. Allergic reactions to a hairdressers' series: Results from 9 European centres. The European Environmental and Contact Dermatitis Research Group (EECDRG). *Contact Dermatitis*. 1993;28(3):180–183.