Amended Safety Assessment of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl as Used in Cosmetics

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*All interested persons are provided 60 days from the above release date (i.e., **November 18, 2023**) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to the Cosmetic Ingredient Review (CIR) will be discussed in open meetings, will be available for review by any interested party, and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.*

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ABBREVIATIONS

ADME	absorption, distribution, metabolism, and excretion
A_{max}	absorbance maximum
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
Dictionary; wINCI	web-based *International Cosmetic Ingredient Dictionary and Handbook*
EC_3	estimated concentrations for a SI of 3
EU	European Union
FDA	Food and Drug Administration
HPLC	high-performance liquid chromatography
LLNA	local lymph node assay
NMR	nuclear magnetic resonance
NOAEL	no-observable-adverse-effect-level
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
SCCP	Scientific Committee on Consumer Products
SED	systemic exposure dose
SI	stimulation index
TG	test guideline
US	United States
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl, which are reported to function as hair dyes in cosmetic products. The Panel reviewed the available data to determine the safety of these ingredients. The Panel concluded that the available data are insufficient to make a determination of safety for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl under the intended conditions of use as hair dye ingredients.

INTRODUCTION

5-Amino-4-Chloro-*o*-Cresol, which according to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*) is reported to function in cosmetics as a hair colorant,[1] was previously reviewed by the Expert Panel for Cosmetic Ingredient Safety (Panel) as part of a safety assessment of 6 amino-cresol hair dye ingredients that was published in 2004.[2] At that time, the Panel concluded that "the available data … support the safety of 5-Amino-4-Chloro-*o*-Cresol… for use in oxidative and nonoxidative (semi-permanent) hair dyes." In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued reports approximately every 15 years, and it has been at least 15 years since this assessment has been issued. In June 2022, the Panel determined that this safety assessment should be re-opened for re-evaluation due to several of the other amino-cresol hair dye ingredients that were included in the original 2004 report being banned for use in cosmetics by the European Commission.[3] However, because the Panel determined that data for these amino-cresol hair dye ingredients could not be read-across, rather than including all 6 ingredients in one amended report, re-reviews of each hair dye will be presented as individual stand-alone reports.

Much of the data on 5-Amino-4-Chloro-*o*-Cresol in the original report was actually on the salt, 5-Amino-4-Chloro-*o*-Cresol HCl. Accordingly, 5-Amino-4-Chloro-*o*-Cresol HCl has been added to this amended report because in situ and in formulation the salt and free base are identical. Excerpts from the summaries of the previous report on 5-Amino-4-Chloro-*o*-Cresol are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized text*. (These data are not included in the tables or the Summary.)

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 July 2023. 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 Cosmetic Ingredient Review (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.

CHEMISTRY

Definition and Structure

According to the *Dictionary*, 5-Amino-4-Chloro-*o*-Cresol (CAS No. 110102-86-8) is the organic compound that conforms to formula in Figure 1.[1] 5-Amino-4-Chloro-*o*-Cresol HCl (CAS No. 110102-85-7) is the hair colorant that is the hydrochloride salt of 5-Amino-4-Chloro-*o*-Cresol. However, the use of regiochemical terms such as "*ortho*-" (i.e., the "-*o*-" in 5-Amino-4-Chloro-*o*-Cresol) is vague and inappropriate when an aromatic system such as a benzene ring has more than 2 substituents. (5-Amino-4-chloro-2-methylphenol is the systematic name for 5-Amino-4-Chloro-o-Cresol).

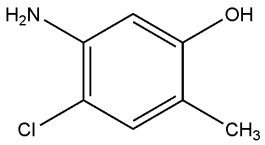

Figure 1. 5-Amino-4-Chloro-*o*-Cresol

5-Amino-4-Chloro-*o*-Cresol HCl is a precursor in oxidative hair dye systems.[4] It reacts with primary intermediates to form the final hair-reactive dye. The reaction can be accelerated by addition of an oxidizing agent (e.g., hydrogen peroxide), but can also be achieved by air oxidation.

Chemical Properties

Chemical properties for 5-Amino-4-Chloro-*o*-Cresol (molecular weight 157.59 g/mol) and 5-Amino-4-Chloro-*o*-Cresol HCl (formula weight 194.06 g/mol) are summarized in Table 1. 5-Amino-4-Chloro-*o*-Cresol is reported to be soluble in water, propylene glycol, and triethanolamine.[2] 5-Amino-4-Chloro-*o*-Cresol has a symmetrical absorption peak below 300 nm, which falls off sharply above 300 nm.

Method of Manufacture

Method of manufacturing data for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

Composition and Impurities

The specification of 97% purity for 5-Amino-4-Chloro-o-Cresol is supported by high-performance liquid chromatography (HPLC) analysis; impurities include an early peak identified as 2-methyl-5-aminophenol (2%), and two unidentified peaks (1% combined), one of which was close to the peak of the ingredient and one that eluted later.[2]

5-Amino-4-Chloro-*o*-Cresol HCl

The purity (general) of 5-Amino-4-Chloro-*o*-Cresol HCl is reported to be > 97% (w/w) through nuclear magnetic resonance (NMR) spectroscopy and > 99% (peak area) through HPLC.[4] Chloride and sulfate content are 18% (w/w) and 0.1% (w/w), respectively. Solvent content as water is < 0.1% (w/w) and as ethanol < 0.3% (w/w). Sulfated ash content is 0.6% (w/w). 4-amino-2-hydroxytoluene (up to 2%) is reported as an impurity. Heavy metal content was reported as the following: lead < 20 ppm; nickel and antimony < 10 ppm; arsenic and cadmium < 5 ppm; and mercury < 1 ppm.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2023 VCRP data[5] and the concentration of use surveys conducted by the Council in 2021 and 2023,[6,7] 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl have no reported uses. When the original safety assessment was published in 2004, 5-Amino-4-Chloro-*o*-Cresol was reported to have no uses, according to 1998 VCRP data.[2] However, according to industry survey data submitted in 1994, 5-Amino-4-Chloro-*o*-Cresol was reported to be used at up to 1% in hair dyes and colors in combination with hydrogen peroxide.

Although products containing this ingredient may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of this ingredient (and without consumer habits and practices data or particle size data related to this use technology), the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

These ingredients are considered coal tar hair dyes 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. 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.[8,9] Hair dye products marketed and sold in the US, though, must follow the labeling requirements established by the Food, Drug, and Cosmetic Act.

In the European Union (EU), 5-Amino-4-Chloro-*o*-Cresol is not specifically restricted from use in cosmetic products, but subject to the general provisions of the EU Cosmetic Regulation.[3] 5-Amino-4-Chloro-*o*-Cresol HCl is categorized in Annex III, the list of substances which cosmetic products must not contain except subject to the restrictions laid down. For this ingredient, the regulation states that the maximum concentration applied to hair must not exceed 1.5% (calculated as hydrochloride) after mixing under oxidative conditions. The Scientific Committee on Consumer Products (SCCP) concluded that 5-Amino-4-Chloro-*o*-Cresol HCl, at a maximum concentration of 1.5% on the head, does not pose a risk to the health of the consumer.[4]

TOXICOKINETIC STUDIES

Dermal Absorption

In Vitro

The dermal absorption/percutaneous penetration potential of [^{14}C]5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) through excised pig skin (750 µm thick) was determined from a cream formulation mixed with a developer containing hydrogen peroxide.[4] The study was performed in accordance with Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 428. The concentration of 5-Amino-4-Chloro-*o*-Cresol HCl in the final application formulation was 1.6%. Using Franz diffusion cells, 20 mg formulation per cm^2 pig skin (dose of test substance was approximately 0.32 mg/cm^2 skin; skin discs were 1.0 cm^2) was applied for 30 min. Application of the test material was terminated by gently rinsing with 0.01% Tween 80 solution and water. The formulation was analyzed in 2 experiments with 4 replicates per experiment for adsorbed, absorbed, and penetrated amount of the test material. The receptor fluid (Dulbecco's phosphate buffered saline; pH 7.35) was analyzed at defined intervals for up to 48 h post-application.

Both the amounts absorbed and penetrated were considered systemically available. The amount of 5-Amino-4-Chloro-*o*-Cresol HCl systemically available from a standard cream formulation mixed with a developer was found to be 12.47 $\pm$ 1.82 µg/cm^2 (range 10.60 to 16.47 µg/cm^2), which is equivalent to 3.90 $\pm$ 0.69% (range 3.12 to 5.29%) of the applied dose. The SCCP stated that the number of chambers used was too few, and therefore an absorbance maximum (A_{max}) of 16.47 µg/cm^2 in an oxidizing formulation (equivalent to 5.29% of the applied dose in a final application formulation containing 1.6% active) was used for the calculation of the margin of safety.[4]

Animal

Skin absorption of [^{14}C]5-Amino-4-Chloro-o-Cresol HCl was studied in female rats.[2] A formulation containing the radiolabeled ingredient (with p-toluenediamine sulfate, basic fatty acid emulsion, propylene glycol, water, and ammonia) was diluted 1:1 with water to make a final test ingredient concentration of 1.85%. The test material was applied for 72 h under semi-occlusive conditions. The amount of ingredient on intact, clipped skin was 0.41 mg/cm^2. The mean skin absorption was 32.7%. 5-Amino-4-Chloro-o-Cresol was excreted via urine (92%) and feces (8%). The concentration in kidneys (0.003%) at 72 h was the greatest of any of the organ/tissue samples. The stratum corneum at the site of application, obtained by tape stripping, had 0.22% of the radioactivity. A similar rat study was performed using the above formulation diluted 1:1 with a developer consisting of 6% hydrogen peroxide before application. The skin absorption in this case was only 1.28%. Excretion via urine (91%) and feces (9%) accounted for all that was absorbed; the concentration in organs/ tissues was at or near the detection limit of the radiolabel. The stratum corneum had 0.2% of the radioactivity and the dermis had 0.2%.

Absorption, Distribution, Metabolism, and Excretion (ADME) Studies

In an oral metabolism study in rats, a 1.27% solution of [^{14}C]5-Amino-4-Chloro-o-Cresol HCl was readily absorbed in the intestine (91.7%).[2] The test material was excreted via urine (94%) and feces (6%). The greatest concentration recovered in the organ/tissue samples was 0.001% in the liver.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

In an acute oral toxicity study, male and female rats received 5-Amino-4-Chloro-o-Cresol HCl by gavage at doses of 1184, 1539, and 2000 mg/kg.[2] For males, the LD_{50} was between 1539 and 2000 mg/kg and for females, the LD_{50} was >2000 mg/kg.

Acute toxicity studies of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl were not found in the updated literature search, and unpublished data were not submitted.

Subchronic Toxicity Studies

Oral

In a 90-d oral study, male and female rats received 5-Amino-4-Chloro-o-Cresol HCl by gavage at doses of 0, 20, 60, and 180 mg/kg/d.[2] No clinical observations or pathological findings indicative of systemic toxicity were observed. Only minor deviations in a few biochemical and hematological parameters were noted. The no-observable-adverse-effect-level (NOAEL) was 180 mg/kg/d.

Repeated-dose toxicity studies of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl were not found in the updated literature search, and unpublished data were not submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

The only maternal effect observed in pregnant rats dosed with aqueous 5-Amino-4-Chloro-o-Cresol HCl (up to 500 mg/kg/d) by gavage on days 6 to 15 of gestation was a brown discoloration of the urine.[2] In fetuses, no developmental toxicity was associated with treatment with 5-Amino-4-Chloro-o-Cresol HCl.

Development and reproductive toxicity studies for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl were not found in the updated literature search, and unpublished data were not submitted.

GENOTOXICITY STUDIES

5-Amino-4-Chloro-o-Cresol was mutagenic with metabolic activation in an Ames test evaluating concentrations of up to 2500 µg/plate of 5-Amino-4-Chloro-o-Cresol HCl dissolved in water and up to 1200 µg/plate of 5-Amino-4-Chloro-o-Cresol dissolved in dimethyl sulfoxide.[2] No increases in the number of mutations were observed in a cell gene mutation test at the HGPRT locus in V79 Chinese hamster lung cells exposed to 5-Amino-4-Chloro-o-Cresol HCl dissolved in ethanol at up to 60 µg/ml without metabolic activation and up to 550 µg/ml with metabolic activation. In an in vivo micronucleus test in mice, 5-Amino-4-Chloro-o-Cresol HCl did not induce micronuclei after a single oral dose of up to 500 mg/kg bw.

Additional in vitro and in vivo genotoxicity studies on 5-Amino-4-Chloro-*o*-Cresol HCl summarized here are detailed in Table 2. In an Ames test, 5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) was mutagenic in strain TA98 with metabolic activation at up to 5000 µg/plate; the test material did not induce an increase in the number of revertant colonies in strains TA100, TA102, TA1535, or TA1537, at any concentration tested, with or without metabolic activation.[4] 5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) was not genotoxic in a L5178 mouse lymphoma cell assay at the *tk* locus at up to 500 µg/ml without metabolic activation or with up to 375 µg/ml with metabolic activation. In an in vitro mammalian cell micronucleus test, a clear dose-dependent increase in cells with micronuclei was observed following exposure of 5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) at up to 1000 µg/ml without metabolic activation and up to 500 µg/ml with metabolic activation in V79 Chinese hamster lung cells. However, an in vivo micronucleus test found that 5-Amino-4-Chloro-*o*-Cresol HCl (purity not reported) did not induce micronuclei in mice that received a single intraperitoneal dose of 500 mg/kg bw.

CARCINOGENICITY STUDIES

Carcinogenicity data for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Animal

Very slight erythema and edema were observed following a 4-h semi-occlusive patch test of 5-Amino-4-Chloro-o-Cresol HCl (concentration not reported) in 3 rabbits.[2] No signs of erythema, edema, eschar formation or systemic toxicity were observed in a 2-h dermal irritation study of a 10% aqueous formulation containing 5-Amino-4-Chloro-o-Cresol HCl in 6 rabbits. In a repeated application study in mice, no primary skin irritation was observed to a 10% dilution of 5-Amino-4-Chloro-o-Cresol HCl, adjusted to pH 8 with ammonia.

The irritation potential of a 10% aqueous solution of 5-Amino-4-Chloro-*o*-Cresol HCl (purity not reported) was assessed in 5 male New Zealand albino rabbits.[10] The test material was adjusted to pH 8 with ammonia and applied as a single dose (0.5 ml) to 6.25 cm^2 intact skin. Occlusive patches were applied and left in place for 4 h. The test sites were then rinsed. The skin was examined for erythema, eschar formation, and edema at 1, 24, and 48 h after the patches were removed. No reactions were observed. It was concluded that a 10% aqueous solution of 5-Amino-4-Chloro-*o*-Cresol HCl was non-irritating.

Sensitization

Animal

5-Amino-4-Chloro-o-Cresol HCl (induced at up to 5% and challenged at 2%; in aqueous solution) was a moderate sensitizer in a guinea pig maximization test.[2] In additional guinea pig maximization tests, formulations containing 5-Amino-4-Chloro-o-Cresol HCl and oxidizing agents (induced at up to 0.2% and challenged at up 20% in formulation diluted 1:1 with 6% hydrogen peroxide) were non-sensitizing. 5-Amino-4-Chloro-o-Cresol in ethanol (63% as paste) was not considered to be a sensitizer in a Buehler guinea pig test.

A local lymph node assay (LLNA) was performed using 5-Amino-4-Chloro-*o*-Cresol HCl (98% pure).[4] Female CBA/CaOlaHsd mice were divided into groups of 4 and received 5, 10, or 20% of the test material in ethanol:water (7:3, v/v) on the ear surface (25 µl) once daily for 3 consecutive days. α-Hexylcinnamaldehyde was used as the positive control and a negative control group received just the vehicle. Five days after the first topical application, all animals were injected intravenously with [^{3}H]methyl thymidine and the proliferation of lymphocytes in the draining lymph nodes was measured. The stimulation indices (SI) were calculated to be 1.18, 0.87, and 0.87 for the 5, 10, and 20% dose groups, respectively. The

estimated concentrations for a SI of 3 (EC_3) was not calculated. The controls yielded expected results. It was concluded that 5-Amino-4-Chloro-*o*-Cresol HCl was not sensitizing when tested at up to 20% in mice.

OCULAR IRRITATION STUDIES

Animal

Aqueous 5-Amino-4-Chloro-o-Cresol HCl (5%) instilled into the conjunctival sac of male albino New Zealand rabbits had no effects on the cornea or the iris, and only slight conjunctival erythema and edema up to 24 h were observed.[2]

In an ocular irritation study performed in accordance with OECD TG 405, 4 male New Zealand White rabbits received 0.1 ml of 5% aqueous 5-Amino-4-Chloro-*o*-Creol HCl (purity not reported) in the conjunctival sac of the right eye.[10] The eye was not rinsed and the left eye served as the control. Ocular reactions were recorded at 1, 6, 24, and 48 h after instillation. Slight redness of the conjunctiva was reported in 3 rabbits within 6 h of instillation, which resolved in all animals by 24 h. Exudate was observed in all rabbits 1 h after instillation, in 3 rabbits after 6 h, and in 1 rabbit until 24 h. No reactions were observed in the cornea or iris. It was concluded that 5% aqueous 5-Amino-4-Chloro-*o*-Cresol HCl was a slight ocular irritant.

In another ocular irritation study, approximately 51 mg of 5-Amino-4-Chloro-*o*-Cresol HCl (> 99% pure) were instilled into the conjunctival sac of one eye in one male New Zealand White rabbit.[4] The eye was not rinsed. The other eye served as the control. The eye irritation reactions were scored 1, 24, 48, and 72 h and 7 d after instillation of the test material. The test material caused severe eye irritation immediately after instillation. Instillation of the test material affected the cornea, iris, and conjunctivae. The opacity of the cornea, injection of the iris, and the irritation of the conjunctivae were irreversible within the study period of 7 d. There was evidence of ocular corrosion and staining with fluorescein revealed corneal epithelial damage in the animal. Under the conditions of the study, undiluted 5-Amino-4-Chloro-*o*-Cresol HCl was extremely irritating to the rabbit eye.

MARGIN OF SAFETY

The SCCP calculated the margin of safety for 1.5% 5-Amino-4-Chloro-*o*-Cresol HCl (on head) under oxidative conditions to be 947.[4] This calculation is based on the NOAEL of 180 mg/kg bw/d from a 90-d oral rat study and a systemic exposure dose (SED) of 0.19 mg/kg bw (skin area surface of 580 cm^2 x absorption through skin of 16.47 $\mu g/cm^2$ x 0.001 (unit conversion)/typical human bw of 60 kg).

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. 5-Amino-4-Chloro-*o*-Cresol and its chloride salt are 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

5-Amino-4-Chloro-*o*-Cresol and its salt, 5-Amino-4-Chloro-*o*-Cresol HCl, are reported to function in cosmetics as hair colorants. 5-Amino-4-Chloro-*o*-Cresol was previously reviewed by the Panel as part of a safety assessment of 6 amino-cresol hair dye ingredients that was published in 2004. At that time, the Panel concluded that according to the available data (in that report), 5-Amino-4-Chloro-*o*-Cresol is safe for use in oxidative and non-oxidative hair dyes. In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued reports approximately every 15 years, and it has been at least 15 years since this assessment has been issued. In June 2022, the Panel determined that this safety assessment should be re-opened for re-evaluation due to several of the other amino-cresol hair dye ingredients that were included in the original 2004 assessment being banned for use in cosmetics by the European Commission.

According to 2023 VCRP survey data, 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl have no reported uses. The results of the concentration of use surveys conducted by the Council in 2021 and 2023 for the free base and the HCl salt, respectively, also reported no uses for these ingredients. When the original safety assessment was published in 2004, 5-Amino-4-Chloro-*o*-Cresol was reported to have no uses, according to 1998 VCRP. However, according to industry survey data submitted in 1994, 5-Amino-4-Chloro-*o*-Cresol was reported to be used at up to 1% in hair dyes and colors (after mixing with hydrogen peroxide).

According to the EU, 5-Amino-4-Chloro-*o*-Cresol is not specifically restricted from use in cosmetic products, but subject to the general provisions of the EU Cosmetic Regulation. 5-Amino-4-Chloro-*o*-Cresol HCl is categorized in Annex III, the list of substances which cosmetic products must not contain except subject to the restrictions laid down. For this ingredient, the regulation states that the maximum concentration applied to hair must not exceed 1.5% (calculated as the

hydrochloride) after mixing under oxidative conditions. The SCCP concluded that 5-Amino-4-Chloro-*o*-Cresol HCl, at a maximum concentration of 1.5% on the head, does not pose a risk to the health of the consumer.

In a dermal absorption/percutaneous penetration study, a cream formulation containing [^{14}C]5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) and hydrogen peroxide was applied to excised pig skin with the final concentration of the radiolabel reported as 1.6%. The amount of 5-Amino-4-Chloro-o-Cresol HCl systemically available was found to be 12.47 $\pm$ 1.82 μg/cm^2 (range 10.60 to 16.47 μg/cm^2), which is equivalent to 3.90 $\pm$ 0.69% (range 3.12 to 5.29%) of the applied dose.

5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) was mutagenic in strain TA98 with metabolic activation in an Ames test at up to 5000 μg/plate; the test material did not induce an increase in the number of revertant colonies in strains TA100, TA102, TA1535, or TA1537, at any concentration tested with or without metabolic activation. 5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) was not genotoxic in a L5178 mouse lymphoma assay at the *tk* locus at up to 500 μg/ml without metabolic activation or with up to 375 μg/ml with metabolic activation. In an in vitro mammalian cell micronucleus test, a clear dose-dependent increase in cells with micronuclei was observed following exposure of 5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) at up to 1000 μg/ml without metabolic activation and up to 500 μg/ml with metabolic activation in V79 Chinese hamster lung cells. However, an in vivo micronucleus test found that 5-Amino-4-Chloro-*o*-Cresol HCl (purity not reported) did not induce micronuclei in mice that received a single intraperitoneal dose of 500 mg/kg bw.

5-Amino-4-Chloro-*o*-Cresol HCl (10% aqueous solution; purity not reported) was non-irritating in a 4 h dermal irritation study in rabbits. In an LLNA, 5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) was not sensitizing when tested at up to 20%. When tested as a 5% aqueous solution, 5-Amino-4-Chloro-*o*-Cresol HCl was a slight ocular irritant to rabbit eyes; however, when instilled undiluted to a rabbit eye, 5-Amino-4-Chloro-*o*-Cresol HCl (> 99% pure) was extremely irritating.

A margin of safety for 1.5% 5-Amino-4-Chloro-o-Cresol HCl (on head) under non-oxidative conditions was calculated to be 947. This calculation was based on an NOAEL of 180 mg/kg bw/d from a 90-d oral rat study and an SED of 0.19 mg/kg bw.

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.

Method of manufacture and carcinogenicity studies on 5-Amino-4-Chloro-*o*-Cresol (or the HCl salt) were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

DISCUSSION

In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued reports approximately every 15 years. In 2004, the Panel published a final report on 5-Amino-4-Chloro-*o*-Cresol and concluded that the available data supported the safety of this ingredient for use in oxidative and nonoxidative (semi-permanent) hair dyes. This report has been reopened for re-evaluation because several of the other amino-cresol hair dye ingredients that were included in the original 2004 report are banned for use in cosmetics by the European Commission. Much of the data on 5-Amino-4-Chloro-*o*-Cresol in the original report was actually on the salt, 5-Amino-4-Chloro-*o*-Cresol HCl. Accordingly, 5-Amino-4-Chloro-*o*-Cresol HCl has been added to this amended report because in situ and in formulation the salt and free base are identical.

In this amended report, the Panel concluded that the available data are insufficient to make a determination of safety for these two hair dye ingredients. To come to a conclusion of safety for these ingredients, the Panel intends to verify the margin of safety for use in hair dyes and will be conducting such calculation based on the available data in this safety assessment. The Panel noted that these ingredients are reported to function as oxidative hair dyes in hair coloring products; however, no use of these ingredients was reported according to 2021 and 2023 concentration of use surveys and 2023 VCRP frequency of use data. In the original (2004) safety assessment, 5-Amino-4-Chloro-*o*-Cresol was reported to be used at up to 1% in hair dyes and colors (after mixing with hydrogen peroxide).

In vitro genotoxicity studies yielded mixed results, and results of in vivo micronucleus studies were negative; however, concern for these mixed results was mitigated by the weight-of-evidence of negative results for other toxicity endpoints. The Panel noted the lack of method of manufacturing information, but data on composition and impurities for these ingredients and the high degree of reported purity obviated this need.

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 Food, Drug, and Cosmetic Act (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.

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.

The Panel's respiratory exposure resource document (available at https://www.cir-safety.org/cir-findings) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the available data are insufficient to make a determination of safety for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol under the intended conditions of use as hair dye ingredients.

TABLES

Table 1. Chemical properties

Property	Value	Reference
	5-Amino-4-Chloro-o-Cresol	
Physical Form	Brown crystals	[2]
Molecular Weight (g/mol)	157.59	[2]
Melting Point (ºC)	248 (decomposition)	[2]
	5-Amino-4-Chloro-o-Cresol HCl	
Physical Form	Beige to light brown amorphous powder	[4]
Formula Weight (g/mol)	194.06	[4]
Boiling Point (ºC)	> 240 (decomposition)	[4]
Water Solubility (g/l @ 20 ºC)	< 1	[4]
Other Solubility (g/l @ 20 ºC)	ethanol: 50-200; dimethyl sulfoxide: > 100	[4]
log P_{ow}	-1.90 (estimated)	[4]

Table 2. Genotoxicity studies

Ingredient	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
			IN VITRO			
5-Amino-4-Chloro-*o*-Cresol HCl; 98% pure	3 - 5000 µg/plate	deionized water	*Salmonella typhimurium* strains TA98, TA100, TA 102, TA1535, TA1537	Bacterial reverse mutation test in accordance with OECD TG 471; with and without metabolic activation	Mutagenic in strain TA98 with metabolic activation; moderate, dose-dependent increase in revertant colonies observed. Toxic effects observed at higher concentrations (not specified) without metabolic activation observed in strains TA98, TA100, TA102, and TA1537, but test material did not induce an increase in number of revertant colonies in the other strains at any concentration tested, with and without metabolic activation. Negative and positive controls in accordance with the guideline	[4]
5-Amino-4-Chloro-*o*-Cresol HCl; 98% pure	Test 1: up to 500 µg/ml without metabolic activation and up to375 µg/ml with metabolic activation Test 2: up to 375 µg/ml without metabolic activation and up to 350 µg/ml with metabolic activation	deionized water	L5178 mouse lymphoma cells	Mammalian cell gene mutation test at the *tk* locus in accordance with OECD TG 476; with and without metabolic activation	Not genotoxic. In cells treated for 4 h without metabolic activation, an increase in the mutant frequency occurred at intermediate dose, but the increase was not reproducible and the mutant frequency was within normal parameters at the higher doses. This effect was not considered biologically relevant. Cells treated for 4 h with metabolic activation had an increase in mutant frequency at highest concentration tested; however, the increase was within historical control range and not reproducible when cells were treated with test material for longer durations or with expression periods. This effect was also not considered biologically relevant. Negative and positive controls were in accordance with the guideline.	[4]
5-Amino-4-Chloro-*o*-Cresol HCl; 98% pure	up to 1000 µg/ml without metabolic activation and up to 500 µg/ml with metabolic activation	deionized water	V79 Chinese hamster lung cells	Mammalian micronucleus test in accordance with draft OECD TG 487 and 473; with and without metabolic activation	Genotoxic; a clear dose-dependent increase in cells with micronuclei observed with and without metabolic activation at concentrations below 250 µg/ml. Precipitation observed at 250 µg/ml and above. Negative and positive controls were in accordance with the guideline.	[4]
			IN VIVO			
5-Amino-4-Chloro-*o*-Cresol HCl; purity not stated	0 and 500 mg/kg bw	distilled water	7 CFW 1 (Winkelmann) mice per sex	Mammalian erythrocyte micronucleus test in accordance with OECD TG 474; single intraperitoneal dose; groups of animals killed at 24, 48, or 72 h post-treatment; appropriate negative and positive controls used	Not genotoxic; test material did not induce micronuclei. No mortalities observed; clinical signs included reduced activity, ruffled fur, and abdominal position; orange colored urine observed after 20 h.	[4]

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