Amended Safety Assessment of 4-Chloro-2-Aminophenol as Used in Cosmetics

Status:	Revised Tentative Amended Report for Public Comment
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*All interested persons are provided 60 days from the above release date (i.e., by **August 17, 2025**) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available for review by any interested party and may be cited in a peer-reviewed scientific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

CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DMSO	dimethyl sulfoxide
DNCB	dinitrochlorobenzene
EPA	Environmental Protection Agency
EU	European Union
FD&C	Food, Drug, and Cosmetic
FDA	Food and Drug Administration
HTS	high-throughput screening
IARC	International Agency for Research on Cancer
JETOC	Japan Chemical Industry Ecology-Toxicology & Information Center
LAI	leukocyte adherence inhibition
LDH	lactate dehydrogenase
MoCRA	Modernization of Cosmetics Regulation Act
NIH	National Institutes of Health
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
RLD	Registration and Listing Data
TG	test guideline
US	United States
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) reassessed the safety of 4-Chloro-2-Aminophenol, which is reported to function as a hair dye ingredient in cosmetic products. The Panel reviewed all data relevant to the safety of this ingredient. The Panel issued an amended report with a revised conclusion stating that 4-Chloro-2-Aminophenol is unsafe for use as a cosmetic ingredient.

INTRODUCTION

4-Chloro-2-Aminophenol, which according to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*) is reported to function in cosmetics as a hair colorant,[1] was previously reviewed by the 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 4-Chloro-2-Aminophenol for use in oxidative hair dyes, but are insufficient to support the safety of…4-Chloro-2-Aminophenol for use in 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 4-Chloro-2-Aminophenol being banned for use in cosmetics by the European Union.[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 were presented as individual stand-alone reports.

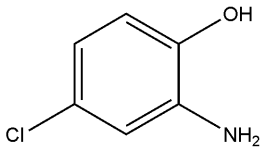
Excerpts from the summaries of the previous report on 4-Chloro-2-Aminophenol are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized text*. (These data are not included in the tables or the Summary.) The original report is available on the Cosmetic Ingredient Review (CIR) website (https://cir-reports.cir-safety.org/).

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 April 2025. 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.

CHEMISTRY

Definition and Structure

According to the *Dictionary*, 4-Chloro-2-Aminophenol (CAS No. 95-85-2) is the hair colorant that conforms to the structure in Figure 1.[1]



Chemical Properties

Chemical properties for 4-Chloro-2-Aminophenol are summarized in Table 1.[4,5] 4-Chloro-2-Aminophenol is a light brown crystalline solid with a molecular weight of 143.57 g/mol.[4] The melting point is 140˚C and the estimated log P_{ow} is 1.24.

Method of Manufacture

4-Chloro-2-Aminophenol is manufactured by converting 2,5-dichloronitrobenzene to 4-chloro-2-nitrophenol in a reaction with sodium hydroxide.[6] The product is then reduced with iron, hydrazine, or hydrogen with Raney nickel or platinum catalyst. It is not known if this method is used for preparation of cosmetic grade products.

Composition and Impurities

The International Agency for Research on Cancer (IARC) Working Group reported that the purity of 4-Chloro-2-Aminophenol to be greater than 95%.[5] No further details were provided. A supplier of 4-Chloro-2-Aminophenol for a subchronic and carcinogenicity study described in those sections of this report stated that their product was > 99.1% pure, and no impurities or degradation products were detected with gas chromatography analysis.[6]

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 4-Chloro-2-Aminophenol in cosmetics. Data included herein were obtained from the FDA and in response to a survey of maximum use concentrations conducted by the

Personal Care Products Council (Council), and it is these values that define the present practices of use and concentration. Frequencies of use obtained from the FDA include data from the Voluntary Cosmetic Registration Program (VCRP) database as well as Registration and Listing Data (RLD). As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was discontinued in 2023 and, as of 2024, 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-year 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] Please note, at this time, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, and because reporting frequency of use is now mandatory (as opposed to the past practice of voluntary reporting). Although the VCRP program is now defunct, trends in frequency of use from the RLD alone are not yet possible in that a baseline is currently not available.

According to 2024 RLD,[8] 2023 VCRP data,[9] and the results of the concentration of use survey conducted by the Council in 2021 (provided in 2022),[10] 4-Chloro-2-Aminophenol has no reported uses. 4-Chloro-2-Aminophenol was also reported to have no reported uses in the original (2004) safety assessment, according to 1998 VCRP data and 1999 industry survey data.[2]

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

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

Product labels shall also bear patch test instructions for determining whether the product causes skin irritation. However, whether or not patch testing prior to use is appropriate is not universally agreed upon. The Panel recommends that an open patch test be applied and evaluated by the beautician and/or consumer for sensitization 48 h after application of the test material and prior to the use of a hair dye formulation. Conversely, a report in Europe suggests that self-testing has severe limitations, and may even cause morbidity in consumers.[11,12] Hair dye products marketed and sold in the US, though, must follow the labeling requirements established by the FD&C Act.

Under European regulations for cosmetic ingredients, 4-Chloro-2-Aminophenol, when used as a substance in hair dye products, is categorized in Annex II, the list of substances prohibited in cosmetic products in Europe.[3]

Non-Cosmetic Use

4-Chloro-2-Aminophenol is reported to be used as an intermediate in the production of dyes used to color textiles and clothing fabrics, leather, and paper chemicals.[5] It is also used in inks and toners. 4-Chloro-2-Aminophenol is reported to be a synthetic precursor of the muscle relaxant chlorzoxazone.[13]

TOXICOKINETIC STUDIES

The IARC Working Group noted that while no experimental data were available on 4-Chloro-2-Aminophenol, it is expected that the material would be absorbed after oral administration and be eliminated via the kidneys.[5] No further details were provided.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Intraperitoneal

Groups of 4 male Fischer 344 rats were given a single intraperitoneal injection of 0.4, 0.8, or 1.2 mmol/kg 4-Chloro-2-Aminophenol hydrochloride in 50% dimethyl sulfoxide (DMSO) in distilled water or vehicle only.[2] *The animals were killed 48 h after dosing. 4-Chloro-2-Aminophenol had very few effects on renal function; no apparent morphological damage was observed at nonlethal doses of <0.8 mmol/kg. Changes in hepatic function or morphology were not observed. A dose of 1.2 mmol/kg 4-Chloro-2-Aminophenol killed 75% of the animals, but little evidence of nephrotoxicity was observed in the surviving animals.*

Subchronic Toxicity Studies

Oral

In a 13-wk study performed in accordance with the Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 408, groups of 10 male and 10 female F344/DuCrlCrlj (Fisher) rats were fed a diet containing 0, 512, 1280, 3200, 8000, or 20,000 ppm 4-Chloro-2-Aminophenol (>99.1% pure).[6] The rats were observed daily for clinical signs of toxicity and mortality. Body weights and feed consumption were measured once a week. Urinalysis was performed near the end of the treatment period, and hematology and blood chemistry analysis were performed at the terminal necropsy. Blood levels of methemoglobin were determined. All animals underwent complete necropsy.

All treated rats of both sexes survived to the end of the 13-wk administration period. Terminal body weight was significantly decreased in the rats of both sexes fed 20,000 ppm and in the male rats fed 8000 ppm. Feed consumption was significantly lowered only in the 20,000 ppm males. Macroscopic examination at terminal necropsy revealed that all male and female 20,000 ppm rats had both enlarged spleens and a thickened forestomach walls. Relative weights of the kidneys and liver were significantly increased in the male rats fed 3200, 8000, or 20,000 ppm 4-Chloro-2-Aminophenol; relative weights of the lungs and spleen were significantly increased in the males given 8000 ppm and greater. The treated female rats exhibited a statistically significant increase in relative spleen and liver weights at 8000 and 20,000 ppm, and in relative kidney weight at 20,000 ppm. A statistically significant increase in methemoglobin levels was observed in the 8000 and 20,000 ppm male rats and in the 20,000 ppm females. A significant increase in reticulocyte counts were observed in males that were fed 1280 ppm or greater of 4-Chloro-2-Aminophenol and in females fed 3200 ppm and above. Red blood cell counts, hemoglobin concentration, and hematocrit were significantly decreased in the males fed ≥ 3200 ppm. In females, red blood cell counts were significantly decreased in the 1280 ppm and above dose groups, while hemoglobin concentration and hematocrit were significantly decreased in the 3200 ppm and above and 8000 ppm and above dose groups, respectively. The plasma level of total bilirubin was significantly increased in the 20,000 ppm dose group of both sexes. No hematuria occurred in any group of either sex.

Histopathological findings included hyperplasia of the forestomach observed in all rats of both sexes that received 8000 and 20,000 ppm of the test material, while the incidence of erosion/ulcer was significantly increased in the females of the 20,000 ppm dose group. In the urinary bladder, the incidence of transitional cell hyperplasia was significantly increased in males of the 20,000 ppm dose group, and two morphologically different types of hyperplasias, i.e., simple and papillary and/or nodular types, were observed. Crystalline or amorphous precipitate could not be detected in the urinary bladder of the 20,000 ppm male rats. Swelling of the transitional epithelium in the urinary bladder, indicating a degenerative change in the transitional cells, occurred in male and female of the 20,000 ppm dose group. A statistically significant incidence of splenic lesions, including hemosiderin deposition, extramedullary hematopoiesis, and erythrocyte engorgement, occurred in both sexes that received ≥ 3200 ppm of the test material. (Extramedullary hematopoiesis was not observed in the 3200 ppm females, but was observed in the 8000 and the 20,000 ppm females). No treatment-related lesions were observed in other organs, including the lungs, kidneys, and liver, in any dose group of either sex. The maximum tolerated dose was determined to be 8000 ppm.[6]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity data for 4-Chloro-2-Aminophenol were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

GENOTOXICITY STUDIES

In Vitro

The mutagenic potential of 4-Chloro-2-Aminophenol in DMSO was determined in a preincubation assay.[2] *Concentrations of 10 to 1500 µg/plate were tested using Salmonella typhimurium strains TA100, TA1535, TA97, and TA98 with and without metabolic activation. 4-Chloro-2-Aminophenol was weakly mutagenic. (No further details were provided.)*

In an Ames test, the mutagenic potential 4-Chloro-2-Aminophenol (99% pure) was tested using *S. typhimurium* strains TA98, TA100, TA1535 and *Escherichia coli* strain WP2uvrA at concentrations up to 5000 µg/plate, with or without metabolic activation.[14] Statistically significant mutagenic effects were observed in strains TA100 and TA1537 with metabolic activation. No further details were provided.

4-Chloro-2-Aminophenol (99.9% pure) induced chromosomal aberrations in Chinese hamster lung cells.[15] The material was tested for 6 h with an 18 h recovery time at up to 0.1 mg/ml without metabolic activation and at up to 0.4 mg/ml with metabolic activation. Without metabolic activation, the material was also tested at up to 0.003 mg/ml for 24 h and 0.006 mg/ml for 48 h, both time periods without recovery time. No further details were provided.

CARCINOGENICITY STUDIES

Since 2019, 4-Chloro-2-Aminophenol has been included on the Proposition 65 list as a chemical known to the state of California to cause cancer.[16] Based on sufficient evidence in experimental animals, IARC stated in a 2020 monograph that 4-Chloro-2-Aminophenol is possibly carcinogenic to humans (Group 2B).[5] The studies that this IARC determination is based on are described below.

In a 2-yr study, groups of 50 male and 50 female B6D2F_1/Crlj mice were fed diets that contained 4-Chloro-2-Aminophenol (> 99.1% pure) at concentrations of 0, 512, 1280, or 3200 ppm (w/w).[17] The mice were observed daily for clinical signs of toxicity and mortality. Body weights and feed consumption were measured once a week for the first 14 wk, and then every 4 wk thereafter. Urinalysis was performed near the end of the treatment period, and hematology and blood chemistry analysis were performed at the terminal necropsy. All mice, including those found dead or in a moribund state as well as those that survived until the end of the 2-yr treatment period, underwent a complete necropsy.

Survival rates, body weights, and feed consumption were similar to controls for all dose groups. In male mice, the incidence of squamous cell papillomas in the forestomach was increased in the 3200 ppm dose group when compared to the control group. Additionally, the incidences of squamous cell papillomas in the forestomach in the males in all the treated groups were higher than

historical control data (statistical significance not reported). A slight increase in the incidence of squamous cell papillomas in the forestomach was also observed in the treated females, but those incidences were within the range of the historical control data. It was concluded that there was evidence of carcinogenic activity in the male mice treated with 3200 ppm 4-Chloro-2-Aminophenol, but there was no evidence of carcinogenic activity from the test material in the female mice.[17]

The same research group performed a carcinogenicity study in groups of 50 male and 50 female Fischer 344/DuCrlCrlj (Fisher) rats.[6,18] The rats were fed a diet containing 4-Chloro-2-Aminophenol (> 99.1% pure) at 0, 1280, 3200, or 8000 ppm for 2 yr. The methodology is the same as described in the mouse study above. Survival rates were similar to controls for all dose groups. There were no statistically significant differences in terminal body weights between any 4-Chloro-2-Aminophenol male dose groups and the male control; however, the 3200 and 8000 ppm females exhibited a statistically significant decrease in terminal body weight compared to the female control. Feed consumption was reduced in a statistically significant manner in the 3200 and 8000 ppm males and the 8000 ppm females. Yellow coloration of the fur was observed in all the male and female treated rats. The incidence of forestomach tumor (squamous cell carcinoma and papilloma) was increased in a statistically significant manner in male rats fed 3200 and 8000 ppm. The incidence of urinary bladder tumor was significantly increased in the 8000 ppm treated males. In females, the incidence of squamous cell papillomas in the forestomach was significantly increased in the 8000 ppm dose group. Non-neoplastic lesions observed included significantly increased incidence of squamous cell hyperplasia of the forestomach in the 3200 and 8000 ppm males and 8000 ppm females. Slight, non-statistically significant changes of anemic parameters including red blood cell count were noted in 3200 and 8000 ppm females, and deposition of hemosiderin in the spleen and significantly increased spleen weights were observed in the 8000 ppm females. It was concluded that there was clear evidence of carcinogenic activity in the male rats treated with ≥ 3200 ppm 4-Chloro-2-Aminophenol, and some evidence of carcinogenic activity from 8000 ppm of test material in the female rats.

High-Throughput Screening Assays

IARC conducted evaluations of bioactivity across various assay endpoints that are commonly associated with carcinogenic potential.[5] Six of 10 identified key characteristics of carcinogens have been examined for 4-Chloro-2-Aminophenol by high-throughput screening (HTS) assays (there are no assays available to test 3 of the characteristics, and no assays were completed to assess one characteristic) used by the US Environmental Protection Agency (EPA) and the US National Institutes of Health (NIH) (Table 2). 4-Chloro-2-Aminophenol was found to be active in 11 of 54 assays run. Specifically, 4-Chloro-2-Aminophenol was considered active in 5 of the 6 assay endpoints linked to the key characteristic of "is genotoxic." Furthermore, 4-Chloro-2-Aminophenol displayed activity in 4 assay endpoints related to the "modulates receptor-mediated effects" characteristic, as well as 1 endpoint associated with the "induces oxidative stress" characteristic and 1 endpoint related to the "alters cell proliferation, cell death, or nutrient supply" characteristic.

OTHER RELEVANT STUDIES

Immunological Effects

The response of leukocytes from female guinea pigs treated with 4-Chloro-2-Aminophenol was evaluated using the leukocyte adherence inhibition (LAI) technique.[2] *Both 4-Chloro-2-Aminophenol and p-aminophenol were conjugated with protein by similar condensation reactions. Significantly greater amounts of LAI were found for p-aminophenol–protein conjugates in the treated guinea pigs, indicating that 4-Chloro- 2-Aminophenol–sensitized lymphocytes could not differentiate between 4-Chloro-2-Aminophenol and p-aminophenol–protein conjugates. This suggested that cross-sensitization can occur with p-aminophenol.*

Nephrotoxicity

Renal cortical slices from male Fischer 344 rats were used in gluconeogenesis and lactate dehydrogenase (LDH) release studies.[2] *The tissue slices were incubated with 0.01 to 0.5 mM 4-Chloro-2-Aminophenol in DMSO or vehicle alone. Renal gluconeogenesis was inhibited by ≥ 0.01 mM 4-Chloro-2-Aminophenol. LDH leakage was increased at concentrations of ≥ 0.5 mM 4-Chloro-2-Aminophenol.*

DERMAL IRRITATION AND SENSITIZATION STUDIES

Dermal Irritation

Dermal irritation data for 4-Chloro-2-Aminophenol were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

Dermal Sensitization

The sensitization potential of 4-Chloro-2-Aminophenol and cross-sensitization potential with p-aminophenol was determined using guinea pigs.[2] *(4-Chloro-2-Aminophenol and p-aminophenol belong to the same amino derivative class and have common side chains on the benzoic ring.) Fifteen female guinea pigs were first injected with an emulsion of 200 mg of 4-Chloro-2-Aminophenol in 0.5 ml N,N-dimethylformamide and 0.5 ml Freund's complete adjuvant. At 2 or 3, 4, and 6 wk after treatment, the animals were patch tested with 0.1, 0.5, and 1.0% 4-Chloro-2-Aminophenol in equal volumes of dioxane and acetone. The solutions, 0.05 ml, were applied to the shaved dorsal area of each animal, and the sites were not covered. The test sites were scored 24 h after application of 4-Chloro-2-Aminophenol. Following patch testing with 4-Chloro-2-Aminophenol, a 1.0% p-aminophenol solution was applied using the same procedure. Five animals that were not treated were patch tested with 4-Chloro-2-Aminophenol and p-aminophenol served as a control group.*

One test animal died by week 6 of the study (reason for death not stated.) At 2 to 3 wk, 1, 1, and 3 of the 15 test animals had reactions (weak or strong erythema) at the 0.1, 0.5, and 1.0% 4-Chloro-2-Aminophenol sites, respectively. During the fourth week of the study, 2, 8, and 13 animals had reactions at the 0.1, 0.5, and 1.0% 4-Chloro-2-Aminophenol sites, respectively. During the sixth week of the study, 2, 7, and 13 of the 14 remaining test animals had reactions at the 0.1, 0.5, and 1.0% 4-Chloro-2-Aminophenol sites, respectively. None of the test animals reacted to p-aminophenol and none of the control animals reacted to 4-Chloro-2-Aminophenol or p-aminophenol.

OCULAR IRRITATION STUDIES

Ocular irritation data for 4-Chloro-2-Aminophenol were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

CLINICAL STUDIES

Occupational

Blood samples were taken from 21 workers that handled 4-Chloro-2-Aminophenol (and other compounds).[2] *Half-oxidized hemoglobins, such as* $(\alpha^{2+}\beta^{3+})_2$ *and* $(\alpha^{3+}\beta^{2+})_2$*, and methemoglobin were significantly increased in circulating erythrocytes of some workers.*

Thirty-one factory workers were patch tested with 4-Chloro-2-Aminophenol, as well as with four other compounds used or produced at the factory.[2] *Using adhesive plasters, 0.1, 0.5 and 1.0% 4-Chloro-2-Aminophenol in petrolatum was applied to the back of each subject for 48 h. The tests sites were scored 20 min after removal of the patches. A challenge test was performed by applying 0.1 ml of 0.1% dinitrochlorobenzene (DNCB) in acetone onto the flexural antebrachium of each person, and the reaction was evaluated 48 h after application. A group of 5 control subjects was tested in the same manner. Of the 31 subjects tested, 7 had positive reactions to all concentrations tested, 6 had positive reactions to 0.5 and 1.0%, 2 had positive reactions to 0.1 and 0.5%, 1 had a positive reaction to 1.0% only, and one had a positive reaction to 0.1 and 1.0% 4-Chloro-2-Aminophenol. Six of the 7 subjects that reacted to all three concentrations of 4-Chloro-2-Aminophenol had been directly exposed to it on repeated occasions. Some cross-sensitization might have occurred between 4-Chloro-2-Aminophenol and the other compounds tested. None of the test subjects had a cross-sensitization reaction with DNCB. None of the control subjects had a primary irritation reaction to any of the tested compounds.*

SUMMARY

4-Chloro-2-Aminophenol is reported to function in cosmetics as a hair colorant. 4-Chloro-2-Aminophenol 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), 4-Chloro-2-Aminophenol is safe for use in oxidative hair dyes; however, the data were insufficient to support safety for use in 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 4-Chloro-2-Aminophenol being banned for use in cosmetics by the European Union.

According to 2024 RLD, 2023 VCRP survey data, and the results of the concentration of use survey conducted by the Council in 2021 (provided in 2022), 4-Chloro-2-Aminophenol has no reported uses. 4-Chloro-2-Aminophenol was also reported to have no reported uses in the original (2004) safety assessment, according to 1998 VCRP data and 1999 industry survey data.

Under European regulations for cosmetic ingredients, 4-Chloro-2-Aminophenol, when used as a substance in hair dye products, is categorized in Annex II, the list of substances prohibited in cosmetic products in Europe.

In a 13-wk study in male and female rats fed a diet containing up to 20,000 ppm 4-Chloro-2-Aminophenol, the maximum tolerated dose was determined to be 8000 ppm. All treated rats survived until study end. Macroscopic findings revealed that all male and females in the 20,000 ppm dose group had both enlarged spleens and thickened forestomach walls. Histopathological findings included hyperplasia of the forestomach in rats of both sexes at 8000 and 20,000 ppm 4-Chloro-2-Aminophenol. Incidences of transitional cell hyperplasia of the urinary bladder were significantly increased in males of the 20,000 ppm dose group. A statistically significant incidence of splenic lesions occurred in both sexes that received ≥ 3200 ppm of the test material. No treatment-related lesions were observed in other organs, including the lungs, kidneys, and liver, in any dose group of either sex.

In an Ames test, 4-Chloro-2-Aminophenol was mutagenic in *S. typhimurium* strains TA100 and TA1537 with metabolic activation when tested at up to 5000 µg/plate. 4-Chloro-2-Aminophenol induced chromosomal aberrations in Chinese hamster lung cells when tested at up to 0.1 mg/ml without metabolic activation and up to 0.4 mg/ml with metabolic activation.

Since 2019, 4-Chloro-2-Aminophenol has been placed on the Proposition 65 list as a chemical known to the state of California to cause cancer. Based on sufficient evidence in experimental animals, IARC determined that 4-Chloro-2-Aminophenol is possibly carcinogenic to humans (Group 2B). A 2-yr mouse study in which animals were fed a diet containing 512 – 3200 ppm 4-Chloro-2-Aminophenol reported increased incidences of squamous cell papillomas in the forestomach of male mice that received 3200 ppm 4-Chloro-2-Aminophenol. Results of a similar study in rats given diets containing 1280 – 8000 ppm 4-Chloro-2-Aminophenol reported increased incidences of squamous cell carcinomas and papillomas of the forestomach in male rats in groups dosed with 3200 and 8000 ppm 4-Chloro-2-Aminophenol. Male rats also had increased incidences of urinary

bladder tumors at 8000 ppm 4-Chloro-2-Aminophenol. Female rats had increased incidences of squamous cell papillomas in the forestomach at 8000 ppm. Non-neoplastic lesions observed included increased incidence of squamous cell hyperplasia of the forestomach in the 3200 and 8000 ppm males and 8000 ppm females. It was concluded that there was evidence of carcinogenic activity in male mice that received 3200 ppm, no evidence of carcinogenic activity in female mice, clear evidence of carcinogenic activity in male rats that received $\geq$ 3200 ppm, and some evidence of carcinogenic activity in female rats that received 8000 ppm 4-Chloro-2-Aminophenol.

HTS assays were utilized to assess the carcinogenic potential of 4-Chloro-2-Aminophenol. This ingredient was active in 11 of 54 assay endpoints.

Developmental and reproductive toxicity, dermal irritation data, and ocular irritation data on 4-Chloro-2-Aminophenol 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 re-evaluates the conclusions of previously-issued reports approximately every 15 years. In 2004, the Panel published a final report on 4-Chloro-2-Aminophenol and concluded that this ingredient was safe for use in oxidative hair dyes. However, the data available at the time were insufficient to support the safety of 4-Chloro-2-Aminophenol for use in non-oxidative (semi-permanent) hair dyes. This report was reopened for re-evaluation due to 4-Chloro-2-Aminophenol being banned for use in cosmetics by the European Commission. In this amended report, the Panel noted a lack of relevant safety data, specifically for the following:

- Maximum concentration of use
- Composition/impurities data
- Toxicokinetics data, especially dermal absorption data
    - If absorbed, additional data, including developmental and reproductive toxicity data, are needed
- Micronucleus genotoxicity data

However, the Panel determined that, while the absorption data is lacking, it is likely that this aromatic amine will absorb to some extent. Additionally, positive genotoxicity results were observed, specifically in Ames tests, along with an increased incidence of urinary bladder tumors in an oral carcinogenicity study in rats. Based on the overall weight of evidence - including the genotoxic potential and tumor findings - the Panel considers that 4-Chloro-2-Aminophenol poses a potential carcinogenic risk to humans, and, therefore, is unsafe for use as a cosmetic ingredient.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that 4-Chloro-2-Aminophenol is unsafe for use as a cosmetic ingredient.

TABLES

Table 1. Chemical properties

Property	Value	Reference
Physical Form	Light brown crystalline solid	[4]
Molecular Weight (g/mol)	143.57	[4]
Density/Specific Gravity (g/ml)	1.41	[5]
Vapor pressure (mmHg @ 25ºC)	0.0015	[4]
Melting Point (ºC)	140	[4]
Water Solubility (g/l @ 20ºC)	3	[4]
log P_{ow}	1.24 (estimated)	[4]

Table 2. Summary of activity of 4-Chloro-2-Aminophenol reviewed in the IARC monograph and tested in ToxCast and/or Tox21 HTS assays.[5]

Key characteristic	Number of positive results out of the number of assays completed*
1. Is electrophilic or can be metabolically activated	0 out of 1
2. Is genotoxic	5 out of 6
3. Alters DNA repair or cause genomic instability	*No assays available*
4. Induces epigenetic alterations	*not tested*
5. Induced oxidative stress	1 out of 3
6. Induces chronic inflammation	0 out of 1
7. Is immunosuppressive	*No assays available*
8. Modulates receptor-mediated effects	4 out of 22
9. Causes immortalization	*No assays available*
10. Alters cell proliferation, cell death, or nutrient supply	1 out of 21
Total hits out of total number of assays evaluated	**11 out of 54**

* Mapped HTS assay endpoints are available to assess 7 of the 10 identified key characteristics.[19]

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