Amended Safety Assessment of 6-Amino-*o*-Cresol as Used in Cosmetics

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All interested persons are provided 60 days from the above release date (i.e., August 26, 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to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to the Cosmetic Ingredient Review (CIR) will be discussed in open meetings, will be available for review by any interested party, and may be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.

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume. This safety assessment was prepared by Christina Burnett, M.S., Senior Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
Da	Daltons
FDA	Food and Drug Administration
FD&C	Federal Food, Drug, and Cosmetic
Panel	Expert Panel for Cosmetic Ingredient Safety
SCCNFP	Scientific Committee on Cosmetic and Non-Food Products
US	United States
VCRP	Voluntary Cosmetic Registration Program
wINCI; *Dictionary*	web-based *International Cosmetic Ingredient Dictionary and Handbook*

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 6-Amino-*o*-Cresol, which is reported to function as a hair colorant in cosmetic products. The Panel reviewed the available data to determine the safety of this ingredient. The Panel concluded that the available data are insufficient to make a determination of safety for 6-Amino-*o*-Cresol under the intended conditions of use as a hair dye ingredient.

INTRODUCTION

6-Amino-*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 six 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 6-Amino-*o*-Cresol… for use in oxidative hair dyes, but are insufficient to support the safety of 6-Amino-*o*-Cresol…in non-oxidative (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 6-Amino-*o*-Cresol 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 now be presented as individual stand-alone reports.

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 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*, 6-Amino-*o*-Cresol (CAS No. 17672-22-9) is the substituted aromatic compound that conforms to formula in Figure 1.[1] However, the use of regiochemical terms such as "*ortho*-" (i.e., the "-*o*-" in 6-Amino-*o*-Cresol) is vague and inappropriate when an aromatic system such as a benzene ring has more than 2 substituents. Thus, a technical name, such as 2-amino-6-methylphenol, is more common in the literature.

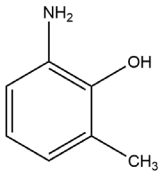

Figure 1. 6-Amino-*o*-Cresol

6-Amino-*o*-Cresol is used as a coupler in oxidative hair dye systems. Couplers, sometimes referred to as color modifiers, react with oxidized hair dye ingredients referred to as precursors. Couplers can react with 2 equivalents of precursor, or if "blocked," react with 1 equivalent of precursor to form trimeric or dimeric-like products, respectively. The methyl group on 6-Amino-*o*-Cresol actively blocks one of those positions; thus, this ingredient reacts with precursors to only form dimer-like products (Figure 2).

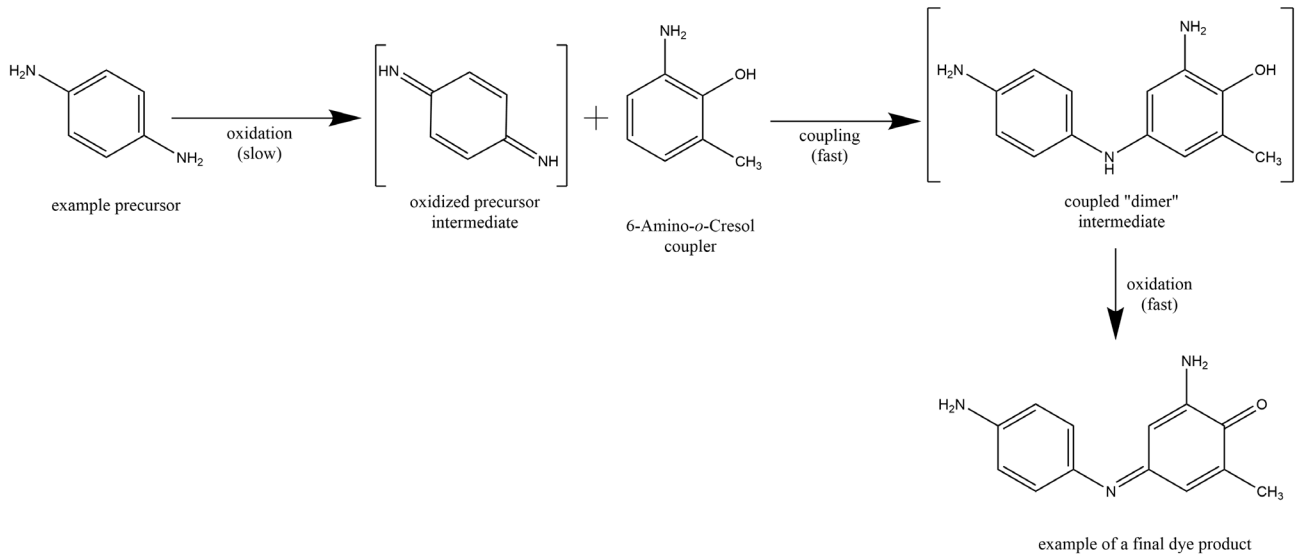

Figure 2. An example (with *p*-Phenylenediamine, in this case) of the oxidative coupling reaction of 6-Amino-*o*-Cresol

Chemical Properties

6-Amino-*o*-Cresol has the molecular weight of 123.07 Daltons (Da).[2] No further chemical properties data were found.

Method of Manufacture

Method of manufacturing data for 6-Amino-*o*-Cresol were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

Impurities

Composition and impurities data of 6-Amino-*o*-Cresol were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

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 this ingredient in cosmetics and does not cover its 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 survey data, 6-Amino-*o*-Cresol has no reported uses.[4] The results of the concentration of use survey provided by the Council in 2022 also report no uses for this ingredient.[5] When the original safety assessment was published in 2004, 6-Amino-*o*-Cresol was reported to have no uses, according to 1998 VCRP data.[2] However, according to industry survey data submitted in 1999, 6-Amino-*o*-Cresol was reported to be used at 0.7% in hair dyes and colors.

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.

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 (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.[6,7] Hair dye products marketed and sold in the US, though, must follow the labeling requirements established by the Food, Drug, and Cosmetic Act.

Under European regulations for cosmetic ingredients, 6-Amino-*o*-Cresol is categorized in Annex II, the list of substances prohibited in cosmetic products in Europe.[3]

TOXICOKINETIC STUDIES

Toxicokinetics studies of 6-Amino-*o*-Cresol were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

TOXICOLOGICAL STUDIES

Acute and repeated-dose toxicity studies of 6-Amino-*o*-Cresol were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity studies of 6-Amino-*o*-Cresol were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

GENOTOXICITY STUDIES

Genotoxicity studies of 6-Amino-*o*-Cresol were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

CARCINOGENICITY STUDIES

Carcinogenicity studies of 6-Amino-*o*-Cresol 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

Dermal irritation and sensitization studies of 6-Amino-*o*-Cresol were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

OCULAR IRRITATION STUDIES

Ocular irritation studies of 6-Amino-*o*-Cresol were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

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. 6-Amino-*o*-Cresol is reported to be used in semi-permanent and 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

6-Amino-*o*-Cresol is reported to function in cosmetics as a hair colorant. 6-Amino-*o*-Cresol was previously reviewed by the Panel in a safety assessment that was published in 2004. At that time, the Panel concluded that 6-Amino-*o*-Cresol was safe for use in oxidative hair dyes, but the data were insufficient to support safety in non-oxidative (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 6-Amino-*o*-Cresol being banned for use in cosmetics by the European Commission.

According to 2023 VCRP survey data, 6-Amino-*o*-Cresol has no reported uses. The results of the concentration of use survey provided by the Council in 2022 also report no uses for this ingredient. When the original safety assessment was published in 2004, 6-Amino-*o*-Cresol was reported to have no uses, according to 1998 VCRP data. However, according to industry survey data submitted in 1999, 6-Amino-*o*-Cresol was reported to be used at 0.7% in hair dyes and colors.

Under European regulations for cosmetic ingredients, 6-Amino-*o*-Cresol is categorized in Annex II, the list of substances prohibited in cosmetic products in Europe.

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.

Toxicokinetics studies, acute and repeated-dose toxicity studies, developmental and reproductive toxicity studies, genotoxicity studies, carcinogenicity studies, dermal irritation and sensitization studies and ocular irritation studies on 6-Amino-*o*-Cresol 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 6-Amino-*o*-Cresol 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 6-Amino-*o*-Cresol for use in non-oxidative (semi-permanent) hair dyes. This report has been reopened for re-evaluation due to 6-Amino-*o*-Cresol being banned for use in cosmetics by the European Commission. In this amended report, the Panel concluded that the available data are insufficient for determining the safety of this ingredient under the intended conditions of use as a hair colorant. The Panel noted a lack of relevant safety data and determined that the data needs from the Insufficient Data Announcement issued following the December 2022 Panel meeting remain unmet. In order to come to a conclusion of safety for this hair dye ingredient, the following additional data are needed:

- Method of manufacture
- Composition and impurities
- Concentration of use
- Absorption, distribution, metabolism, and excretion studies
    - If absorbed, developmental and reproductive toxicity studies, genotoxicity studies, and potentially other endpoints may be needed

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 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 6-Amino-*o*-Cresol under the intended conditions of use as a hair dye ingredient.

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