Post Meeting Announcement

Expert Panel for Cosmetic Ingredient Safety
167th Meeting (December 4 - 5, 2023) - Findings

December 8, 2023

● Final Safety Assessments

- **5-Amino-4-Chloro-*o*-Cresol – 2 ingredients – Safe as hair dyes**
- **Charcoal– 3 ingredients – Safe**

● Tentative Safety Assessments

- **1,2,4-Trihydroxybenzene – 1 ingredient – Safe as a hair dye**
- **Yeast – 56 ingredients – Split conclusion (11 Safe; 22 Safe w/qualifications; 23 Insufficient data)**
- ***p*-Phenylenediamine – 3 ingredients – Safe as hair dyes**
- **MIBK – 1 ingredient – Safe w/qualifications**

● Insufficient Data Announcement

- **Prostaglandins – 2 ingredients**

● Tabled Report

- **Octoxynols – 25 ingredients**

● 167th Meeting Notes

- **Director's Report and Presentations**
- **Re-Reviews – 2 conclusions reaffirmed**
- **Re-Review summaries – 4 approved**
- **Inhalation Resource Document**
- **Nitrosation Resource Document**
- **Tools Strategy**
- **Scientific Literature Reviews – available or under development**
- **Next Expert Panel Meeting – Thursday and Friday, March 28-29, 2024**

Final Safety Assessments

Final safety assessments will be posted on the Cosmetic Ingredient Review (CIR) website at www.cir-safety.org. Unpublished data cited as references in CIR safety assessments are available for review. Any interested person who has sound scientific evidence that a final safety assessment is incorrect may petition the Expert Panel for Cosmetic Ingredient Safety (Panel) to amend the safety assessment.

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

The Panel issued a Final Amended Report with the conclusion that 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl are safe for use as hair dye ingredients in the present practices of use and concentration described in the safety assessment. The Panel previously reviewed 5-Amino-4-Chloro-*o*-Cresol as part of a larger group of amino cresol hair dyes; however, because the Panel determined that data for these amino cresol hair dye ingredients could not be read across the group, re-reviews of each hair dye included in that original 2004 report are now 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 is included in this amended report because in situ and in formulation, the salt and free base are identical.

5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl are reported to function as oxidative hair dyes in hair coloring products. While no uses are currently reported, previous use data indicated 5-Amino-4-Chloro-*o*-Cresol was used at 1% in hair dyes and colors. The Panel recognizes that hair dyes containing these ingredients, as coal tar hair dye products, are exempt from certain adulteration and color additive provisions of the US 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.

While results of in vivo micronucleus studies were negative, in vitro genotoxicity studies yielded mixed results; however, concern for these mixed results was mitigated by the weight-of-evidence (WoE) 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 mitigated this need. The Panel performed a conservative margin of safety (MOS) calculation using the assumption of 50% absorption of 5-Amino-4-Chloro-*o*-Cresol HCl and daily application. The resulting MOS for 5-Amino-4-Chloro-*o*-Cresol HCl formulated at 1% is 217, which is considered protective.

Plant-Derived Charcoal Ingredients

The Panel issued a Final Report with the conclusion that the following 3 plant-derived Charcoal ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

Charcoal Charcoal Extract Charcoal Powder

These ingredients, as used in cosmetics, comprise carbonaceous materials produced by the pyrolysis of plant-derived organic matter. Only plant-derived charcoal ingredients are included in this assessment; accordingly, charcoal derived from petroleum or other mineral sources are excluded from this review. The International Nomenclature Committee (INC) has determined that activated charcoal is a synonym for Charcoal Powder, and is listed as such in the *Dictionary*.

Tentative Safety Assessments

For the tentative safety assessments listed below, to be posted on the CIR website (https://www.cir-safety.org) in the near future, interested persons are given 60 days from the posting date to comment, provide information, and/or request an oral hearing before the Panel. 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 and are available for review by any interested party. Please submit data and/or comments to CIR ***as soon as possible, but no later than 60 days from the actual posting date of the report, for full consideration. Submissions received thereafter may be in jeopardy of not being considered by the Panel.*** *The updated reports may be scheduled for review by the Panel as early as at the* ***March 28-29, 2024*** *meeting. However, it is likely that some of these updated reports may not be scheduled for review until the June 3-4, 2024 meeting.*

1,2,4-Trihydroxybenzene

The Panel issued a Tentative Report for public comment with the conclusion that 1,2,4-Trihydroxybenzene is safe for use as a hair dye ingredient in the present practices of use and concentration described in the safety assessment. According to 2023 VCRP survey data, this ingredient is reported to be used in 18 hair dye formulations and 1 hair shampoo (coloring). The results of the concentration of use survey conducted by the Council indicate 1,2,4-Trihydroxybenzene is used at up to 2.5% in hair dyes and colors.

1,2,4-Trihydroxybenzene is reported to function as an oxidative hair dye in hair coloring products. 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 noted that while results of in vivo micronucleus studies were negative, in vitro genotoxicity studies yielded mixed results; however, concern for these mixed results was mitigated by the WoE of negative results for other toxicity endpoints. The Panel performed a conservative MOS calculation using lowest-observed-adverse-effect-level (LOAEL) of 50 mg/kg bw/d as a Point of Departure (PoD), an assessment factor of 3 for extrapolation from LOAEL to no-observed-adverse-effect-level (NOAEL), and the dermal absorption per treatment of 2.5% Trihydroxybenzene of 2.15 mg. The resulting MOS is 466, well above the accepted risk threshold of 100, and is considered protective.

Yeast-Derived Ingredients

The Panel issued a Tentative Report for public comment with a split conclusion of safety for these 56 yeast-derived ingredients. Ingredients in which both dermal sensitization data and food use/generally recognized as safe (GRAS)/qualified presumption of safety (QPS) status were considered safe in the present practices of use and concentration described in the assessment. These ingredients include the following:

Hydrolyzed Candida Saitoana Extract
Galactomyces Ferment Filtrate
Hydrolyzed Metschnikowia Agaves Extract
Metschnikowia Agaves Extract
Hydrolyzed Metschnikowia Reukaufii Extract
Metschnikowia Reukaufii Lysate Extract
Phaffia Rhodozyma Extract
Phaffia Rhodozyma Ferment Extract
Pichia Anomala Extract
Pichia Minuta Extract
Saccharomyces Cerevisiae Extract

Also considered safe were the following 22 generic-named yeast-derived ingredients (ingredients in which the species of yeast used in manufacturing was not provided in the *Dictionary*), when derived from species of yeast included in the report, with both dermal sensitization and food use/GRAS/QPS status.

Hydrolyzed Saccharomyces Cell Wall
Hydrolyzed Saccharomyces Extract
Hydrolyzed Saccharomyces Lysate Extract
Hydrolyzed Yeast
Hydrolyzed Yeast Extract
Lactic Yeasts
Pichia Extract
Saccharomyces
Saccharomyces Extract
Saccharomyces Ferment
Saccharomyces Ferment Extract
Saccharomyces Ferment Extract Lysate Filtrate
Saccharomyces Ferment Filtrate
Saccharomyces Ferment Lysate Extract
Saccharomyces Ferment Lysate Filtrate
Saccharomyces Lysate
Saccharomyces Lysate Extract
Saccharomyces Lysate Extract Filtrate
Saccharomyces Lysate Filtrate
Yeast
Yeast Extract
Yeast Ferment Extract

It should be noted that data remain insufficient to conclude on the safety of the generic ingredients listed above when the species used to manufacture these ingredients do not have dermal sensitization data and food use/GRAS/QPS status. Data were also considered insufficient for the following 23 ingredients:

Hydrolyzed Candida Bombicola Extract
Hydrolyzed Kluyveromyces Extract
Hydrolyzed Metschnikowia Shanxiensis
Hydrolyzed Torulaspora Delbrueckii Extract
Kluyveromyces Extract
Lipomyces Lipid Bodies
Lipomyces Oil
Lipomyces Oil Extract
Metschnikowia Henanensis Extract
Metschnikowia Viticola Extract
Pichia Caribbica Ferment
Pichia Ferment Extract Filtrate
Pichia Ferment Lysate Filtrate
Pichia Heedii Extract
Pichia Pastoris Ferment Filtrate
Schizosaccharomyces Ferment Extract Filtrate
Schizosaccharomyces Ferment Filtrate
Schizosaccharomyces Pombe Extract
Torulaspora Delbrueckii Extract
Torulaspora Delbrueckii Ferment
Yarrowia Lipolytica Extract
Yarrowia Lipolytica Ferment Lysate
Yarrowia Lipolytica Oil

These ingredients were insufficient with regard to one or more of: systemic toxicity data, food use/GRAS/QPS status, and dermal sensitization data. Both systemic toxicity data (via a 28-d dermal toxicity assay) and dermal sensitization data are needed to conclude on the safety of these ingredients (food use/GRAS/QPS status may be used in lieu of systemic toxicity data). It should be noted that if 28-d dermal toxicity data are provided and these data indicate absorption of the ingredient, other toxicity endpoints would be required to determine safety (e.g., developmental and reproductive toxicity).

_p_-Phenylenediamine, _p_-Phenylenediamine HCl, and _p_-Phenylenediamine Sulfate

The Panel issued a Tentative Amended Report for public comment with the conclusion that the following ingredients are safe for use as hair dye ingredients in the present practices of use and concentration described in the safety assessment:

p-Phenylenediamine *p*-Phenylenediamine HCl *p*-Phenylenediamine Sulfate

According to 2023 VCRP survey data, *p*-Phenylenediamine is reported to be used in 200 formulations. The majority of these uses are in hair coloring preparations; however, 7 uses have been reported for eye makeup preparations. Only 1 use was reported in a hair coloring shampoo for the HCl salt and no uses were reported for the sulfate salt. The results of the concentration of use survey conducted by the Council in 2022 indicate *p*-Phenylenediamine has a maximum concentration of use range of 0.98 - 3% in hair dyes, with a maximum on-head concentration after dilution of 1%. No concentrations of use were reported for related salts.

With regard to the reported use in eye makeup preparations, the FD&C Act mandates that color additives must be approved by FDA for their intended use before they are used. The Panel has also noted that *p*-Phenylenediamine has been used as a dye in black henna temporary tattoos. *p*-Phenylenediamine is an unapproved color additive in cosmetics products (including in eye makeup preparations and tattoos), and thereby, such uses are not permitted according to the Act. These uses are not within the purview of this Panel.

These ingredients are reported to function as oxidative hair dyes in hair coloring products. The Panel recognizes that hair dyes containing these ingredients, 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.

MIBK

The Panel issued a Tentative Amended Report for public comment with the conclusion that MIBK is safe as used in nail care products and as an alcohol denaturant in cosmetics in the present practices of use and concentration described in the safety assessment.

At the June 2023 meeting, an Insufficient Data Announcement (IDA) on MIBK was issued. Concentration of use and function, in aftershave formulations, and confirmatory sensitization studies at the maximum use concentration, were requested. No new data was received or found. The Panel noted that use in the aftershave product is safe if the function is as an alcohol denaturant. Additionally, the Panel reiterated that when used as an alcohol denaturant, MIBK should not be used at more than 4%.

Insufficient Data Announcement

For this insufficient data announcement, interested persons are given an opportunity to comment, provide information, and/or request an oral hearing before the Panel. 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 and are available for review by any interested party. Please submit data and/or comments to CIR ***as soon as possible, but no later than April 26, 2024, for full consideration****.* ***Submissions received thereafter might not be considered by the Panel at their next meeting.*** *This report may be scheduled for review by the Panel as soon as the* ***June 3-4, 2024 meeting****.*

Prostaglandin Analogues

The Panel issued a second IDA for Isopropyl Cloprostenate and Ethyl Tafluprostamide. In order to determine the safety of Isopropyl Cloprostenate, the Panel requires the following data:

- dermal irritation and sensitization data at the current maximum concentration use of 0.0075%
- data on local ocular effects (intraocular pressure, iris color change, and periorbital fat loss) at current maximum concentration of use
    - independent ophthalmologist to assess colorimetric data regarding iris color change
- acute toxicity data
- repeated dose toxicity data
- developmental and reproductive toxicity data
- in vitro and in vivo genotoxicity data

In order to determine the safety of Ethyl Tafluprostamide, the Panel requires:

- acute toxicity data
- repeated dose toxicity data
- developmental and reproductive toxicity data
- in vivo genotoxicity data

Fulfillment of the above data needs is preferred; however, the Panel noted suggestions from industry regarding the use of read-across source to fill in toxicological data gaps for these prostaglandin ingredients. The Panel acknowledged they would consider confirmatory data (e.g., receptor interaction studies and downstream profiles of adverse effects) to determine if the use of the proposed read-across sources is appropriate to target the ingredients in this report. Lastly, robust information on possible targets and mechanisms regarding these ingredients are requested for both Isopropyl Cloprostenate and Ethyl Tafluprostamide.

Tabled Report

For this Tabled Report, interested persons are given an opportunity to comment, provide information, and/or request an oral hearing before the Panel. 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 and are available for review by any interested party. Please submit data and/or comments to CIR ***as soon as possible for full consideration****. This report may be scheduled for review by the Panel as soon as the* ***September 30 - October 1, 2024 meeting****.*

Octoxynols

The Panel determined that the Draft Amended Report of the following 25 octoxynol ingredients should be tabled until updated use data are available via reporting in the Cosmetics Direct database, as mandated in a forthcoming initiative of the Modernization of Cosmetic Regulation Act of 2022 (MoCRA).

Octoxynol-1
Octoxynol-3
Octoxynol-5
Octoxynol-6
Octoxynol-7
Octoxynol-8
Octoxynol-9
Octoxynol-10
Octoxynol-11
Octoxynol-12
Octoxynol-13
Octoxynol-16
Octoxynol-20
Octoxynol-25
Octoxynol-30
Octoxynol-33
Octoxynol-40
Octoxynol-70
Octoxynol-9 Carboxylic Acid
Octoxynol-20 Carboxylic Acid
Potassium Octoxynol-12 Phosphate
Sodium Octoxynol-2 Ethane Sulfonate
Sodium Octoxynol-2 Sulfate
Sodium Octoxynol-6 Sulfate
Sodium Octoxynol-9 Sulfate

167th Meeting Notes

Director's Report

Dr. Heldreth thanked the members of and liaisons to the Expert Panel for Cosmetic Ingredient Safety. He noted that for this meeting, CIR had taken a couple of steps to make the workload more manageable, including reducing the number of reports in progress and placing a firm cut-off for late submissions. He also confirmed that these steps would continue to be utilized.

CIR and the Panel have previously discussed the value and relevance of the MoCRA legislation of 2022, and how quickly the deadline to submit ingredient registrations was looming. Fortunately, this deadline has been pushed back until July 2024. Additionally, along with the updated regulatory authority provided by MoCRA, FDA is proposing a ban on the use of formaldehyde in hair-straightening formulations, in full agreement with this Panel's conclusion in the Formaldehyde and Methylene Glycol report. This is particularly important as these products are targeted at certain communities, and it is paramount that these consumers are protected. CIR applauds this progress.

As a member of the CIR Steering Committee, the president of the Personal Care Products Council (PCPC) plays an important role as a member therein. Dr. Heldreth stated that CIR and the Panel have been fortunate to have Lezlee Westine in that role over the last decade, who played a major role in the MoCRA legislation. Lezlee will be retiring at the end of this year and Tom Myers, currently PCPC's Executive Vice President for Legal & Regulatory Affairs and General Counsel, will be the Council's new president starting in 2024. Dr. Heldreth stated that he has been fortunate to consult with Tom over the years, and wanted to express how very fortunate CIR and the Panel are to have him stepping into these new roles.

On the agenda at this meeting were 5 speakers covering 1,2,4-Trihydroxybenzene and Prostaglandins. First up was Dr. AJ Cuevas, Combe Sr. Manager Global Product Safety, who delivered a presentation titled "1,2,4-THB – Comprehensive Review of Chemical & Toxicological Data CIR Expert Panel Meeting." Following a Q&A session thereon, Mr. Craig Weiss, President CPTC, and Mr. David Abramovitz, Partner Locke Lord, presented "New Studies Support Safety of Isopropyl Cloprostenate in Cosmetics." Finally, Dr. Thomas Petry, Managing Director ToxMinds BVBA and Ms. Sanghamitra Mishra, ERT, Senior Consultant at ToxMinds presented "Safety Assessment of Ethyl Tafluprostamide as Used in Cosmetic Products." Following these presentations, there were 8 reports advancing in the review process with a great deal of input from the speakers. There were also a number of administrative items, including resources documents on Nitrosation and Inhalation, and a Strategy Memo regarding various in silico tools. The CIR Staff have already started investigating some of the new in silico tools, with plans to investigate more to better support this Panel.

Re-Reviews

In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued safety assessments approximately every 15 years. At this meeting, the Panel considered 2 previous assessments for re-review. In both cases, the Panel reaffirmed the conclusions reached for these safety assessments (choosing to not re-open the original reports). A re-review summary will be presented to the Panel for each of these safety assessments at an upcoming meeting.

- Sodium Carbonate – 3 ingredients
- VA/Crotonates Copolymer – 1 ingredient

Re-Review Summaries

Once the Panel determines to not reopen a previously-issued safety assessment, thereby reaffirming the existing conclusion, a re-review summary is prepared. The Panel approved the following 4 re-review summaries:

- Zinc Phenolsulfonate
- Isobutane
- Laneth-10 Acetate
- Sodium Dehydroacetate

Inhalation Resource Document

The Panel reviewed the revised Inhalation Resource Document and discussed the newly incorporated particle size data of certain propellant-driven sprays. The Panel noted spray products associated with innovative formulations and advanced nozzle techniques may release aerosols with increasing proportion of respirable particles (e.g., dry shampoo and airbrush devices). The Panel recognized the importance of characterizing the relevant spray devices and better understanding the advancement of analytical methods to accurately examine the particle size distribution under realistic use conditions. The Panel will closely monitor the new particle size distribution data of these products, along with the development of analytical techniques for measuring the fine and ultrafine particles emitted by sprayable cosmetic products. The Panel contemplated requesting more information and clarification about device application and exposure parameters from industry and the FDA Office of Devices. Following the acquisition of further information and input, the Panel plans to revise the respiratory boilerplate language to reflect their comprehension of the risks associated with incidental inhalation. Furthermore, the Panel will implement further editorial revisions for enhancing the document's conciseness and readability.

Nitrosation Resource Document

The Panel reviewed a revised Nitrosation Resource Document and agreed to open it for a 60-day period of public comment. The Panel expressed their appreciation to Dr. Ron Shank for his invaluable contribution in revising the document. The Panel further discussed the necessity of clarifying certain strategies for minimizing nitrosation, which are recommended for formulators, as well as the necessity of clarifying the presence of certain nitrosatable precursors which may exist as impurities in raw materials. Upon considering and addressing any feedback received during the public comment period, this document will be presented to the Panel again for further review.

Tools Strategy

The Panel discussed the possible application of certain in silico tools identified by the CIR Science and Support Committee (SSC) for searching data and assessing the risk and safety of cosmetic ingredients. The Panel further discussed the limitations of in silico assessments in terms of reliability and relevance for data gap filling. The Panel agreed results obtained from certain in silico tools would be considered as additional resources in a WoE approach to derive robust conclusions.

Scientific Literature Reviews

The following Scientific Literature Reviews (SLRs) are either posted at the CIR website or are currently under development, and may be posted imminently. These may then be presented to the Panel for their review (as Draft Reports) during the next few meetings.

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Copper Gluconate
HC Blue No. 15
Inositol
Nelumbo nucifera-derived ingredients
Paeonia suffruticosa-derived ingredients
Pyridoxine and Pyridoxine HCl

Next Expert Panel Meeting

Thursday and Friday, March 28-29, 2024, to be held ***virtually*** **(**platform to be determined). Please check the CIR website for details as the meeting approaches. The link will be available approximately a month before the meeting and will be found on the 168th meeting page of the CIR website. https://www.cir-safety.org/