Post Meeting Announcement

Expert Panel for Cosmetic Ingredient Safety
168th Meeting (March 28 - 29, 2024) - Findings

April 3, 2024

● Final Safety Assessments

- **None**

● Tentative Safety Assessments

- **4-Amino-*m*-Cresol – 1 ingredient – Safe as a hair dye**
- **Lanolin – 9 ingredients – Safe**
- **Toluene – 1 ingredient – Safe with qualifications**
- **MIBK – 1 ingredient – Safe with qualifications**
- **Pentapeptides – 3 ingredients – Safe**
- **BHA – 1 ingredient – Safe**
- ***t*-Butyl Alcohol – 1 ingredient – Safe**

● Insufficient Data Announcement

- **Copper Gluconate – 1 ingredient**

● 168th Meeting Notes

- **Director's Report**
- **Re-Review – 1 reopened (Pyrogallol)**
- **Re-Review summaries – 2 approved (Sodium Carbonate & VA/Crotonates Copolymer)**
- **Read-Across Working-Group**
- **Exposure and Risk**
- **Draft Priorities**
- **Phthalates Strategy**
- **Scientific Literature Reviews – available or under development**
- **Next Expert Panel Meeting – Monday and Tuesday, June 3-4, 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 Unpublished data cited as references in CIR safety assessments are available for review.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.

None

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 All unpublished data submitted to CIR will be discussed in open meetings and are available for review by any interested party.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 at the next review.*** *The updated reports may be scheduled for review by the Panel as early as at the* ***June 3-4, 2024*** *meeting. However, it is likely that some of these updated reports may not be scheduled for review until the September 30 – October 1, 2024 meeting.*

4-Amino-*m*-Cresol

The Panel issued a Tentative Amended Report for public comment with the conclusion that 4-Amino-*m*-Cresol is safe for use as a hair dye ingredient in the present practices of use and concentration described in the safety assessment. The Panel previously reviewed this ingredient 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.

4-Amino-*m*-Cresol 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 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 noted that the available toxicokinetic studies show that 4-Amino-*m*-Cresol absorbs slowly through the skin, is not genotoxic, is not a developmental or reproductive toxicant, is not a dermal irritant, and has low concentrations of use. Additionally, a margin of safety (MOS) calculation yielded a result greater than 100, which is generally considered to be protective. However, the Panel further deliberated on incorporating the skin absorption data presented in the report for calculating the MOS, rather than relying on the conservative estimate of 50% absorption. The Panel considered these findings, coupled with the short exposure time as a rinse-off product, and determined that the data are sufficient to conclude that 4-Amino-*m*-Cresol is safe as a hair dye ingredient in the present practices of use and concentration.

Lanolin-Derived Ingredients

The Panel issued a Tentative Amended Report for public comment with the conclusion that the following 9 lanolin-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment:

Acetylated Lanolin	Hydroxylated Lanolin	Lanolin Alcohol
Acetylated Lanolin Alcohol	Lanolin	Lanolin Oil
Hydrogenated Lanolin	Lanolin Acid	Lanolin Wax

The Panel discussed the "lanolin paradox" where Lanolin may cause allergic contact dermatitis when applied to damaged skin, but allergenicity does not appear in these apparently sensitized patients when Lanolin is applied to normal, healthy skin in patch tests. The rate of allergic reaction to Lanolin is extremely low in the general population, and sensitization can be further reduced when Lanolin is ultra refined to reduce the amount of free Lanolin Alcohol. The Panel cautioned that Lanolin should not be used on damaged skin, especially in high-risk populations for sensitivity (e.g., pediatric and geriatric populations).

Toluene

The Expert Panel issued a Tentative Amended Report for public comment with the conclusion that Toluene is safe at up to 20% in nail products. According to 2023 VCRP survey data, Toluene is not reported to be used; however, the 2023 concentration of use survey conducted by the Personal Care Products Council (Council) indicate that Toluene is used at up to 20% in nail polish and enamel. Other uses were reported in the survey at low concentrations; however, these concentrations refer to Toluene as an impurity in cosmetic products and are thus not relevant to the purposes of this report.

The safety of this ingredient in nail products was supported by a lack of irritation and sensitization in human assays and conservative MOS calculations yielding values above 100. However, the Panel requested additional MOS calculations be conducted by using a point of departure (POD) for the developmental and reproductive toxicity (DART) endpoint. The Panel noted the potential for Toluene to result in reproductive and endocrine toxicity; however, this concern was mitigated as these effects were observed at high concentrations not relevant to cosmetic exposure. (It was also noted that occupational exposure is not within the purview of the Panel.) The Panel also noted regulations from the California Department of Toxic Substances Control (DTSC) mandating that manufacturers of nail products certify that their products do not contain more than 100 ppm Toluene. After review of the data for each endpoint, the Panel could not come to the conclusion that Toluene should not exceed 100 ppm in nail products, and instead determined that Toluene is safe in nail products at the current maximum use concentration of 20%.

MIBK

The Panel issued a Revised Tentative Amended Report for public comment concluding that MIBK is safe as used in nail polish removers and as an alcohol denaturant in cometic products. The Panel determined that the use of MIBK as an alcohol denaturant in cosmetic products should not be more than 4% MIBK in alcohol; it was emphasized that this usage should not be misconstrued as not more than 4% MIBK present in a final

formulation. The Panel also noted that the reports of MIBK-induced renal changes observed in studies were due to a male rat specific mechanism of action and should not be considered a human health concern.

Pentapeptides

The Panel issued a Tentative Report for public comment with the conclusion that Myristoyl Pentapeptide-4, Palmitoyl Pentapeptide-4, and Pentapeptide-4 are safe in cosmetics in the present practices of use and concentration described in the safety assessment. The amino acid sequence of the pentapeptide portion of these ingredients can vary; one sequence is lysine-threonine-threonine-lysine-serine (i.e., Lys-Thr-Thr-Lys-Ser, or KTTKS), and the other is Lys-Thr-Ser-Lys-Ser (or KTSKS). The Panel found the information in the report sufficient to apply the conclusion to both sequences.

The Panel noted that although human repeated insult patch tests (HRIPT) were not performed at maximum use concentrations, the negative results obtained in these studies, in conjunction with the negative results observed in chemico and in vitro, mitigated any concern regarding sensitization. Additionally, the negative human dermal irritation studies at less than the maximum use concentration were supported by a negative in vitro study. The Panel also considered the low reported maximum concentration of use for these ingredients, limited percutaneous absorption in the skin, negative genotoxicity data, absence of endocrine disruption at a concentration of 0.12%, and method of manufacturing and impurities data for Palmitoyl Pentapeptide-4. Furthermore, the Panel considered their previous safety review of the individual amino acids, as well as myristic acid and palmitic acid, comprising these ingredients which were determined to be safe as used in cosmetics.

BHA

The Panel issued a Tentative Amended Report for public comment with the conclusion that BHA is safe in cosmetics in the present practices of use and concentration described in the safety assessment. A safety assessment on BHA was first published in 2005, with a conclusion of safe as a cosmetic ingredient in the present practices of use (as described in the safety assessment); that conclusion was reaffirmed, as published in 2006. A re-review was initiated at the June 2023 Panel meeting to evaluate potential endocrine and reproductive effects of BHA at high doses and to provide an updated assessment of the safety of this ingredient.

The Panel concurred with the Discussion presented in the original (1984) report. In addition, the Panel considered the developmental and reproductive toxicity and endocrine studies presented in the updated report, and stated that any developmental and reproductive, endocrine, androgenic, and estrogenic effects that were observed were seen primarily in cell systems and at non-physiological concentrations, thus mitigating any concerns. The Panel also noted the generally recognized as safe (GRAS) for use in foods in the US, and stated that the exposure assessment included in the document was useful when evaluating safety.

***t*-Butyl Alcohol**

The Panel issued a Tentative Amended Report for public comment with the conclusion that *t*-Butyl Alcohol is safe in cosmetics in the present practices of use and concentration described in the safety assessment. The last safety assessment on this ingredient was published in 2005, with a conclusion of safe as used in cosmetic products. A re-review was initiated at the September 2023 Panel meeting to evaluate developmental and reproductive toxicity effects seen at 1% (which is comparable to the highest reported concentration of use), to update the previous discussion of carcinogenicity, and to rectify the erroneous test concentration stated in a previously reviewed HRIPT.

The Panel determined that a negative guinea pig maximization test mitigated a need for confirmatory sensitization data at maximum concentration of use. The Panel discussed the carcinogenicity studies and determined that the weight-of-evidence does not support a carcinogenic effect. Also, the Panel was in agreement with the Discussion in the 2005 report which stated that effects of *t*-Butyl Alcohol on development were likely secondary to maternal toxicity and effects on learning development were attributed to *t*-Butyl Alcohol in maternal milk and were not an in utero effect. Finally, the Panel noted that because undiluted *t*-Butyl Alcohol was an ocular irritant, ocular irritation data at maximum use concentration would add to the robustness of the safety assessment.

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 June 2, 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* ***September 30 – October 1, 2024 meeting****.*

Copper Gluconate

The Panel issued an insufficient data announcement (IDA) for Copper Gluconate. The additional data needed to determine the safety of this ingredient are:

- Impurities data for Copper Gluconate as used in cosmetics
- Dermal irritation and sensitization data at maximum concentration of use
- Ocular irritation data, if available

168th Meeting Notes

Director's Report

Dr. Heldreth thanked the members of and liaisons to the Panel. He noted that a new sub-group of the Panel, the CIR Read-Across Working-Group, held an initial meeting on the general topic of read-across. The Panel also reviewed administrative items regarding exposure, risk, priorities, and

strategies for the review of Dibutyl Phthalate. With specific note on Dibutyl Phthalate and future ingredient re-reviews wherein use has been discontinued, he noted a proposal to the CIR Steering Committee to add a new conclusion category of "use not supported," citing lack of use and concentration data. At this meeting, the Panel also welcomed a new CIR Senior Scientific Analyst, Dr. Thushara Diyabalanage.

Re-Review

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 the previous assessment of Pyrogallol for re-review. The Panel reopened this safety assessment to incorporate and discuss the findings of the National Toxicology Program 2-year carcinogenicity study that was published in 2013, as well as any additional relevant data that has been published since the report was last reviewed. The Panel noted that this hair dye ingredient has only one reported use in hair coloring products and no reported concentrations of use. The Panel advised that current use (frequency and concentration) data and dermal irritation test data at up to the previously reported maximum use concentration of 5% are needed to aid the Panel in determining a potential revised conclusion. A Draft Amended Report will be presented to the Panel for this safety assessment at a future meeting.

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 2 re-review summaries:

- Sodium Carbonate
- VA/Crotonates Copolymer

Read-Across Working-Group – "…30% chemistry, 70% context…."

The Panel has been utilizing read-across strategies for a number of years. One early example can be found in the Alkyl PEG Ethers report, affording the safety assessment of 369 ingredients in one report, even though there were data gaps for numerous ingredients therein (if read-across was not used). With the trend away from new animal studies and toward new approach methodologies (NAMs), the necessity of utilizing read-across strategies is ever increasing. And the complexities of these strategies are often well beyond simple interpolations between various length straight-chain hydrocarbons or various numbers of ethoxy repeat units.

At this 1st meeting of the Read-Across Working-Group (RAWG), the Panel Chairperson, Dr. Wilma Bergfeld, appointed Panel member, Dr. Allan Rettie, as the chair of the RAWG. The RAWG comprises Dr. Rettie, as well as Drs. Tilton, Klaassen, and Ross. As a sub-group of the Panel, the RAWG does not make any final ingredient safety decisions or even vote (when acting as the sub-group). Instead, this sub-group is charged with determining what parameters are needed, on a case-by-case (report-by-report or ingredient-by-ingredient) basis, and to propose a threshold of confidence (or lack thereof) to the full Panel, wherein a read-across strategy is utilized. Essentially, the RAWG is charged in each case with determining if the provided data and associations between read-across source(s) and target(s) are sufficient and valid, and that there is a consensus of confidence (or lack thereof) in the strategy for filling a specific data gap. The members of the RAWG agreed to these notions and will proceed with supporting the full Panel with their analyses of such strategies, on a case-by-case basis.

Exposure and Risk

The Panel reviewed an exposure assessment strategy memo and endorsed the integration of exposure assessments into CIR reports whenever feasible. The Panel agreed that transparent estimates of exposures across different product categories are crucial for effectively assessing risk. The Panel further discussed the need and feasibility of estimating cumulative exposures from multiple product categories compared to identifying and clarifying a single category that poses the highest systemic exposure.

The Panel also reviewed the CIR Science and Support Committee's (SSC's) comments and reached a consensus that the inclusion of a quantitative systemic risk assessment should be determined on a case-by-case basis. The Panel acknowledged the significance of transparent exposure and systemic risk assessments; in cases where a margin of safety is deemed not applicable, the Panel asks for an explanation to be provided in the discussion to ensure transparency and clarity. Additionally, the Panel recognizes that the need for margins of safety can vary depending on endpoints of concern and should be established based on valid points of departure (e.g., NOAELs and LOAELs), which are identified and substantiated by the data included in the report.

Draft Priorities

There are 18 reports docketed, covering 31 ingredients, on the 2024 Final Priorities List. Reports previously prioritized and on the CIR docket, as well as an extensive number of re-reviews of previous assessments, will supplement the total number of reports/ingredients to be assessed in 2024, and beyond. Additionally, with modernization efforts to better utilize in silico tools (e.g., DEREK), NAMs, Cosmetics Direct (the US FDA mandatory reporting program to replace the now defunct voluntary program, VCRP), formalized exposure and risk assessments (when warranted), and read-across (including proposals of the RAWG), CIR proposed that there is plenty of substance on the Panel's docket to extend through the end of 2025.

The Panel agreed with the proposal to make no frequency-of-use-based ingredient report additions to the Panel's docket in the coming year. However, if any interested party would like to request an ingredient review for cause (including: highlighting a potential risk/safety concern, accompanied with supporting data/information), CIR would be happy to present these to the Panel for potential prioritization. To make a request for cause, please provide a complete submission to CIR no later than May 3rd, 2024.

Phthalates Strategy

The Panel discussed the strategy of the preparation of the Draft Amended Report for Dibutyl Phthalate. The Panel reopened the report on this ingredient in 2023 after the FDA petitioned the Panel to accelerate its re-review. The Panel determined that Diethyl Phthalate and Dimethyl Phthalate should be included in the safety assessment as much of the published literature involves data on these ingredients together; however, the Panel stressed that any use, exposure, or risk data from one ingredient could not be read-across to the other ingredients in the report, citing in part

very different use conditions from one ingredient to the next. The Panel also offered guidance on the presentation of the data, especially data relating to endocrine effect, in the updated safety assessment.

Additionally, the Panel discussed the current regulatory status of Dibutyl Phthalate in the European Union and in several US states. The Panel requested clarification on the status of these regulations, and the data that support such.

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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Basic Blue 7
Cannabidiol
Inositol
Nelumbo nucifera-derived ingredients
Paeonia suffruticosa-derived ingredients
Pyridoxine and Pyridoxine HCl
Trimethylbenzoyl Diphenylphosphine Oxide

Next Expert Panel Meeting

Monday and Tuesday, June 3-4, 2024, to be held ***in-person***, at the Westin Georgetown, 2350 M St., NW, Washington, DC 20037. Please check the CIR website for details as the meeting approaches. A link will also be available, for observation-only of the meeting, virtually, approximately a month before the meeting and will be found on the 169th meeting page of the CIR website. https://www.cir-safety.org/