Wave 3
Communications Supplement

ADMIN Draft Priorities

ADMIN Hair dye

5-Amino-4-Chloro-o-Cresol

5-Amino-6-Chloro-o-Cresol

Basic Blue 99

Clays

Hyaluronates

Mallow

Trisodium Ethylenediamine Disuccinate

REREVIEWS

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EXPERT PANEL MEETING
MARCH 6-7, 2023

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: February 24, 2023

SUBJECT: 2024 Draft CIR Priorities

The Personal Care Products Council respectfully submits the following comments on the 2024 draft CIR priorities.

Cannabis Sativa Seed Oil (hemp seed oil) should not be reviewed in the same report as Cannabidiol (CBD). This article from Medical News Today https://www.medicalnewstoday.com/articles/hemp-seed-oil-vs-cbd-oil explains the difference between CBD and hemp seed oil. CBD is extracted from the stalks, leaves and flowers of hemp, while as the name implies, hemp seed oil is from the seeds and contains "omega-6 and omega-3 fatty acids, gamma-linolenic acid, and other nutritional antioxidants. It is also high in B vitamins and vitamin D." It contains no tetrahydrocannabinol "and little to no CBD". Reviewing these ingredients in separate reports would also be consistent with past CIR reviews in which specific substances isolated from plants are reviewed separately from the complex mixtures of other ingredients derived from the plant.

The link to the 2000 SCCNFP opinion on Basic Blue 7 from the EU Commission website goes to the main committee page, not the opinion (checked on February 23, 2023). Has CIR staff found a copy of the SCCNFP opinion on this ingredient?

It should be noted that Basic Blue 9 is methylene blue, a drug used to treat methemoglobinemia.

The EU status of Tetrabromophenol Blue in the priorities document is not correct. There is a 2019 SCCS opinion (https://health.ec.europa.eu/system/files/2021-08/sccs_o_232_0.pdf) (rather than the 2012 opinion cited in the priorities document) with a conclusion of "safe when used as a hair dye in oxidative and non-oxidative hair colouring products at a final on-head concentration of up to 0.2%". Tetrabromophenol Blue has also been added to EU Annex III (entry 319) with the limitations recommended by the SCCS in 2019.

Bismuth Citrate should not be reviewed by CIR staff because it is a US FDA approved colorant (a color additive exempt from certification) (see 21CFR73.2110 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=73.2110). Based on CIR procedures, Bismuth Citrate can be excluded from CIR assessment.

It is not necessary to include the EU trivial name Propolis Cera as an additional ingredient in the CIR report. This is just the labeling name for Propolis Wax in Europe. The CIR report should indicate that Propolis Cera and Propolis Wax are two names for the same ingredient.

As the root/rhizome of *Curcuma longa* is used to make the spice turmeric, the CIR report should be limited to ingredients derived from the root/rhizome. In addition to the Root Extract, Root Oil, Root Powder and Rhizome Extract suggested by CIR staff, the report should also include Rhizome Juice, Rhizome Oil, Root, Root Juice and Root Water.

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TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: February 24, 2023

SUBJECT: Hair Dye Epidemiology Resource Document (draft prepared for the March 2023 meeting)

The Personal Care Products Council (PCPC) respectfully submits the following comments on the Hair Dye Epidemiology Resource Document considered during the March 2023 meeting of the Expert Panel for Cosmetic Ingredient Safety.

Key Issue
Please delete the quote from the American Cancer Society from the background section ("the US National Toxicology Program (an interagency program of the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the US Food and Drug Administration (FDA)) classifies some chemicals that are or were used in hair dyes as 'reasonably anticipated to be human carcinogens'"). If this is left in the document, please add specific information. What are the hair dyes included in NTP's list of materials "reasonably anticipated to be human carcinogens"?

Additional Considerations
Background – It would be helpful to add "California's" before "Office of Environmental Health Hazard Assessment".

Multiple Cancer Types – Please correct "perspective" to "prospective"

Breast Cancer – In the first paragraph of the Breast Cancer section, the study is called the "Sister Study". The last paragraph of this section calls it the Eberle et al. 2020 study. It would be helpful to call this study (reference 26) the same name throughout this document.

Breast Cancer – In the last paragraph ""wer" needs to be corrected to "were"

Hematologic Cancers – Please revise the following sentence ("was identified" should be deleted and it would be clearer if it was at least 2 sentences): "When analysis stratified by ever hair dye

us [should be “use”] before or after 1980, there was no associated risk with DLBCL was identified, the OR was 2.75 (95% CI: 0.91 - 8.29) and 0.56 (95% CI: 0.22 - 1.45) for ever hair dye use <1980 for hair dye use only ≥1980, respectively.”

Pediatric Germ Cell Tumors – Did the questionnaire used in reference 69 include questions on topics in addition to hair dye use? Did the authors indicate how serum perfluorohexane sulfonate was related to hair dye use?

Testicular Cancer – It would be helpful to present the section on testicular cancer after the section on prostate cancer.

Uterine Cancer – It would be helpful to present the section on uterine cancer after the section on ovarian cancer. “opinions” should be corrected to “options”

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: February 27, 2023

SUBJECT: Draft Amended Report: Safety Assessment of 5-Amino-4-Chloro-o-Cresol and 5-Amino-4-Chloro-o-Cresol HCl as Used in Cosmetics (draft prepared for the March 2023 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft amended report, Safety Assessment of 5-Amino-4-Chloro-o-Cresol and 5-Amino-4-Chloro-o-Cresol HCl as Used in Cosmetics.

Key Issue
It is misleading to state that in Europe "5-Amino-4-Chloro-o-Cresol is not restricted from use in cosmetic products." It would be clearer to state: it is "not specifically restricted from use in cosmetic products, but subject to the general provisions of the EU Cometic Regulation". This includes the EU labeling requirements for hair dyes which should be included in this report.

Additional Considerations
Introduction – Please correct "ae" to "are"

Definition and Structure – The CIR report states that use of "ortho" for a benzene ring with more than 2 substituents is not appropriate. Please state the "appropriate" name for this ingredient.

ADME, old report summary – If they only measured radioactivity and did not confirm that the radioactivity represented the parent compound, it would be clearer if "It" was changed to "Radioactivity".

Genotoxicity; Summary – Please correct: "The test material did not include an increase…" ("include" should be "induce")

Margin of Safety; Summary – Although not specifically stated in the opinion, the margin of safety description should note that the SED was calculated assuming use of a product containing 1.5% 5-Amino-4-Chloro-o-Cresol (as included in the question to the Committee).

Table 2 – When there is only one (or a few) FDA product categories with reported uses, presenting use by FDA product category is sufficient. Presenting the summary information with predominantly NR or NA does not provide any useful information.

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TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: February 24, 2023

SUBJECT: Draft Amended Report: Safety Assessment of 5-Amino-6-Chloro-o-Cresol as Used in Cosmetics (draft prepared for the March 2023 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft amended report, Safety Assessment of 5-Amino-6-Chloro-o-Cresol as Used in Cosmetics.

Key Issue
Cosmetic Use; Summary - Please do not rely on COSING for EU regulatory information; especially when something seems to be missing. Please check the actual regulation. The COSING user guide disclaimer states: "The Institutions do not assume any liability for the content of this database. Only information provided by Cosmetics Regulation (EC) No 1223/2009, and its amendments, have a legal value." The statement that there is no concentration limit for this ingredient in oxidative dyes is wrong. The actual regulation (2013/1197/EC https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32013R1197) states that Annex III 283 has a limit of 1% "after mixing under oxidative conditions" (found in the "other" column of the regulation) in addition to the 0.5% limit in non-oxidative products. It would also be helpful if the EU hair dye labeling requirements were included in the CIR report.

Additional Considerations
Definition and Structure – The CIR report states that use of "ortho" for a benzene ring with more than 2 substituents is not appropriate. Please state the "appropriate" name.

Dermal Absorption, In Vitro – Please correct "SCCP" to "SCCS".

Subchronic –Please state the dose(s) for the recovery group.

Margin of Safety, Summary – As the SCCS was asked for their opinion about the safety of using 5-Amino-6-Chloro-o-Cresol in hair dyes (oxidative and non-oxidative) at 2%, the SED values were calculated assuming use at 2%. This should be stated in the Margin of Safety section and the Summary.

Table 2 – For ingredients used in just a few FDA cosmetic product categories, such as hair dyes, presenting the use information by FDA product category is sufficient.

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Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: February 27, 2023

SUBJECT: Draft Amended Report: Safety Assessment of Basic Blue 99 as Used in Cosmetics (draft prepared for the March 2023 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft amended report, Safety Assessment of Basic Blue 99 as Used in Cosmetics.

Key Issue
Cosmetic Use; Summary – It is misleading to state that in Europe "there are no restrictions for the use of Basic Blue 99". It would be clearer to state: it is "not specifically restricted from use in cosmetic products, but subject to the general provisions of the EU Cometic Regulation". This includes the EU labeling requirements for hair dyes which should be included in this report.

Additional Considerations
Irritation, In Vitro – Please revise: "To measure cell viability measurement,"

Table 2 – For an ingredient with use in a limited number of FDA cosmetic product categories, the summary by exposure type is not necessary.

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TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: February 24, 2023

SUBJECT: Draft Final Report: Safety Assessment of Naturally-Sourced Clays as Used in Cosmetics (draft prepared for the March 2023 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft final report, Safety Assessment of Naturally-Sourced Clays as Used in Cosmetics.

Key Issues

Another SCCS Opinion on aluminum in cosmetics was finalized on February 1, 2023. This opinion (at: sccs_o_266.pdf (europa.eu)) should be added to the Cosmetic Use section.

Acute, Inhalation, Parenteral, Illite, Montmorillonite, Kaolin; Cytotoxicity, Illite, Montmorillonite, Kaolin – It is not clear if the studies on the environmental samples of dust that also contain about 20% quartz (reference 39) are relevant to the cosmetic ingredients under review. If the Expert Panel considers this reference to be relevant to the report, please make it clearer that environmental samples were used. The descriptor "naturally-occurring" is being used for other clay cosmetic ingredients which are cleaned and processed. One example is the chronic oral study of a Montmorillonite clay (called "naturally-occurring") that is used as an anti-caking agent in animal feed. There appears to have been no treatment of the "dust" that was studied in reference 39 – it is clearly not a cosmetic ingredient (or an ingredient used in food).

Additional Considerations

Summary - If reference 39 is kept in the report, it should clearly state that environmental dust samples were studied and that the dust contained approximately 20% quartz. It should also be stated that the Montmorillonite clay used in the chronic oral study was a material used as an anti-caking agent in animal feed.

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TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: February 24, 2023

SUBJECT: Draft Report: Safety Assessment of Hyaluronates as Used in Cosmetics (draft prepared for the March 2023 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft amended report, Safety Assessment of Hyaluronates as Used in Cosmetics.

Introduction – Rather than saying that the literature search was done from "2004 forward", it would be helpful to at least state the year the search was completed so that it is clear when the report is published after it is finalized.

Impurities – The units for endotoxin are not correct. The references (12, 13) said: "EU/mg [which is mg of the ingredient]" not "EU/mg bacterial endotoxins" as stated in the CIR report.

Penetration Enhancement, old report summary – It is not clear if this paragraph is discussing the penetration of Hyaluronic Acid or diclofenac in the presence of Hyaluronic Acid.

DART, old report summary – As the time of dosing relative to gestation/mating determines the type of DART study, please be more specific about the types of studies that were completed. This can be done by stating the guideline that was followed or the dosing period relative to gestation.

Carcinogenicity Studies, old report studies – The studies in this section are not carcinogenicity studies. They discuss the possible role of Hyaluronic Acid in cancer, not the potential for Hyaluronic Acid to cause cancer. The information from the old Discussion is helpful and puts these studies into perspective.

Other Relevant Studies – Unless they were studying egg whites, "egg albumen and dog albumen" needs to be corrected to "egg albumin [the protein in egg whites] and dog albumin".

Dermal Irritation and Sensitization; Summary; Table 10 – The concentration of Hydrolyzed Sodium Hyaluronate (FW<1kDa) was 1% - it should not state "concentration not reported".

Summary – It is more appropriate to call a study in which animals were exposed only during gestation a developmental toxicity study rather than a reproductive toxicity study.

Summary – Since the *in vitro* assays do not actually measure "sensitization" it would be clearer to state that "No responses predicting sensitization were noted…" Please state the concentrations of Hydrolyzed Sodium Hyaluronate and Sodium Hyaluronate tested in the *in vitro* phototoxicity assays.

Summary – The Summary should make it clear that case reports of reactions to Hyaluronic Acid used as an injectable dermal filler are not included in the report. The case reports that are included concern Hyaluronic Acid used to treat osteoarthritis.

Tables 4 and 5 – Are the rows containing no information necessary? These rows associated with an FDA product category with no uses reported should be deleted in the final CIR report.

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Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: February 24, 2023

SUBJECT: Draft Final Report: Safety Assessment of *Malva sylvestris* (Mallow)-Derived Ingredients as Used in Cosmetics (draft prepared for the March 2023 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft final report, Safety Assessment of *Malva sylvestris* (Mallow)-Derived Ingredients as Used in Cosmetics.

Composition and Impurities, Malva Sylvestris (Mallow) Extract – The units for GAE and total flavonoid content should be stated per g of sample.

Composition and Impurities, Malva Sylvestris (Mallow) Flower/Leaf/Stem Extract – This section should be revised to make it clear that the extracts of various plant parts were being analyzed, rather than the leaves, flowers, immature fruits, and leafy flowered stems (reference 16).

Composition and Impurities, Malva Sylvestris (Mallow) Leaf Extract – The description of reference 23 should also be revised to indicate that the extract of leaves (rather than "leaves extracted") were analyzed for phenolic and flavonoid content.

Cosmetic Use – In the following, it appears that an FDA eye area product category is missing after "6": "are reported to be used in products applied near the eye, in 6 and 2 other eye makeup preparations".

Summary – In the paragraph on the anti-inflammatory study (TPA application). What were the "other compounds"?

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TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: February 24, 2023

SUBJECT: Draft Final Report: Safety Assessment of Trisodium Ethylenediamine Disuccinate and Tetrasodium Iminodisuccinate as Used in Cosmetics (draft prepared for the March 2023 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft final report, Safety Assessment of Trisodium Ethylenediamine Disuccinate and Tetrasodium Iminodisuccinate as Used in Cosmetics.

Toxicokinetics; Summary – The results of a toxicokinetic study should always be stated with some indication of the time after dosing. At what timepoint after dosing was the mean radioactivity content of blood and tissue 0.136% and 0.153% (male and female rats)? At what timepoints were the peak levels of radioactivity found in the testes, kidneys, liver, and bone marrow?

DART; Summary – The dosing period in relation to gestation needs to be stated for each DART study. To state that the rats were treated for 70 d is not sufficient. Table 7 states that the rats were treated for 70 before mating and they were treated during mating and gestation. In the text of the DART section and the Summary, it should also be stated that in addition to being treated before mating, the rats were treated during mating and gestation.

Dermal Irritation and Sensitization – It should be stated that the ingredients were tested moistened.

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TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: February 24, 2023

SUBJECT: March 2023 Re-Reviews (drafts prepared for the March 2023 meeting)

The Personal Care Products Council (PCPC) respectfully submits the following comments on the re-reviews considered during the March 2023 meeting of the Expert Panel for Cosmetic Ingredient Safety.

Dioscora Villosa (Wild Yam) Root Extract

Key Issue
The Expert Panel was concerned with diosgenin levels in the original report. Therefore, it would have been helpful to note whether or not the levels of diosgenin were stated for the material tested in each new study.

Additional Considerations
Acute – The dose used in this study was 5 g/kg, not 5 mg/kg as stated in the table.

Short-term – Were there any other endpoints examined in this study?

Hormonal effects – The table says “menopausal” while the memo says “premenopausal”

MIBK

It would be helpful to add a statement in the memo or another line in the table about the status of the re-review ingredients in Europe. The 2004 CIR report states that MIBK is not prohibited for use in Europe. This has changed, it is now listed in Annex II – prohibited.

ADME, Hirota – What did they measure in the urine? What are the units for MIBK?

Dermal Irritation and Sensitization – Both guinea pig studies found in the ECHA dossier did not find any evidence of sensitization, but the “different” column says “Yes, sensitization was not

reported in the original report". This column should say "No" (not different from the original report), as no sensitization was reported in the new studies.

Use Table – When few to no uses are reported, the use information should only be presented by FDA cosmetic product category. The summary information with mostly NR is not helpful.

Stearalkonium Chloride

Key Issue
The memo incorrectly states the EU limit in rinse-off hair products as 0.3%. It is correctly stated as 3% in the table. Please check the regulation, rather than relying on COSING. The COSING user guide disclaimer states: "The Institutions do not assume any liability for the content of this database. Only information provided by Cosmetics Regulation (EC) No 1223/2009, and its amendments, have a legal value." The actual regulation (2000/6/EC https://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX%3A32000L0006) states that Annex III 65 also has a limit of 0.1% for products other than rinse-off hair products.

Additional Considerations
Non-Cosmetic Use – Stearalkonium Chloride is not an adhesive. It is approved for use as a component of adhesives. It should be made clear that 21CFR176.300 is for slimicides used as components of paper and paperboard.

Subchronic, Oral – Based on the information in the table, it is not clear if any dogs in the subchronic oral study "died" (it seems that the word "died" in the table should be "diet"). The ECHA dossier indicated that none of the dogs died. The dossier also provides the doses at the tested concentrations (0, 8, 25 and 50 mg/kg bw/day for males and 0, 9, 26, 45 mg/kg/day for females at 0, 500, 1500 and 3000 ppm in the diet, respectively) which should be stated.

Dermal Irritation, In vitro – To be consistent with the presentation of other studies, it should state that the ingredient had a cationic activity of 96.2%.

Dermal Irritation, animal – This should be "Dermal Sensitization – animal". The species used and the number (guinea pig, n=6) should be stated.

Propylene Carbonate

Subchronic Oral – Propylene Carbonate (incorrectly called "Propylene Glycol" in this row) was given in deionized water, it was not "undiluted". It may be clearer if the purity of the test material was stated.

Subchronic Inhalation – Regarding the eye effects in the subchronic inhalation study, the ECHA dossier states that they were also observed at high frequency in the controls so the significance of the observation in the exposure groups were considered "dubious".

No Comments

PCPC has no comments on the following re-review documents:
Polyamino Sugar Condensate
Sweet Almond Seed Meal

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: February 24, 2023

SUBJECT: March 2023 Re-Review Summaries (drafts prepared for the March 2023 meeting)

The Personal Care Products Council (PCPC) respectfully submits the following comments on the re-review summaries considered during the March 2023 meeting of the Expert Panel for Cosmetic Ingredient Safety.

HC Yellow No. 5

Please revise: "reported to the VCRP in 2022". The non-hair dye uses were also included in the 2021 VCRP, so they were not "reported to the VCRP in 2022". The VCRP data received by CIR in 2022 includes information reported to the VCRP over many years, not just in 2022.

Use Table – When uses are reported in only a few FDA product categories, only the use table by FDA product category is needed.

No Comments

PCPC has no comments on the following re-review summaries:
Choleth-24
Methyl Alcohol
Peanut Glycerides
Phytantriol