Wave 3 Supplement

Hair Dye Epi

Benzophenones March

Diacetone Alcohol

Phosphorylcholine Polymers

Sage

Saccharide Humectants

Coconut

Papaya

Silicates

Red algae

Pearce 2019

CIR EXPERT PANEL MEETING
March 11-12, 2021

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: March 9, 2021

SUBJECT: Expert Panel Resource Document: Hair Dye Epidemiology (draft prepared for the March 11-12, 2021 meeting of the Expert Panel for Cosmetic Ingredient Safety)

The Personal Care Products Council respectfully submits the following comments on the Expert Panel Resource Document: Hair Dy Epidemiology.

Key Issue

Page 8, the Sisters study - The 45% higher breast cancer risk in black women was for subjects reporting use of permanent hair dye in the 12 months before study enrollment. However, as presented in Table 3 of the study, no significant association is seen between permanent hair dye use and breast cancer risk when durations of use ('years of personal use') are considered. The adjusted hazard ratio for black women reporting >5 years of permanent hair dye use is 0.97 (95% CI 0.70,1.34); for those reporting <5 years the HR is 1.08 (0.77,1.52). The adjusted hazard ratio in white women reporting >5 years of permanent hair dye use is 1.06 (0.97,1.16); for those reporting <5 years, the HR is 1.10 (0.97,1.24).

Additional Considerations

Background – The first sentence about the IARC review should also mention animal studies, as animal studies are mentioned later.

Study Summary – Please delete the word "recently" in the summary of the new prospective study (reference 8), as it will not apply a few years from now.

Lymphoma and Leukemia – "DCBCL" should be revised to "DLBCL"

In the summary of reference 27, please clarify if the children, or the parents of the children with leukemia used hair dyes.

In the summary of reference 18 in both the text and table it states: “Multivariable regression analysis indicated that parents use of hair dye during breastfeeding..” Did the really indicate “parents” or should this just be “mothers”?

Page 6, 1st (incomplete) paragraph – “…when all studies were combined, the OR value was 1.14 (95% CI: 1.01 - 1.29), indicating that the risk of NHL in a high population of hair dye users was 14%.” This statement needs re-wording – what is high, the number of hair dye users, or their use of hair dyes?

In the summary of reference 29, please revise the following sentence: “The results suggested that people who used more than 20 years of hair dye had increased risk of NHL.” To “The results suggested that people who used hair dyes for more than 20 years had increased risk of NHL.”

Glioma – Please revise: “cohort studies of personal was conducted to investigate the hair dye use and the incidence of gliomas” to “cohort studies were conducted to investigate personal hair dye use and the incidence of gliomas”

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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: March 8, 2021

SUBJECT: Draft Final Amended Report: Safety Assessment of Benzophenones as Used in Cosmetics (draft prepared for the March 11-12, 2021 meeting of the Expert Panel for Cosmetic Ingredient Safety)

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

Supplementary data – The SCCS opinion should not be added to the CIR report until after the SCCS opinion is finalized.

Introduction; Discussion – The following statement is misleading as it suggests that the Expert Panel for Cosmetic Ingredient Safety was waiting for NTP studies on more than one benzophenone ingredient: "results from National Toxicology Program (NTP) carcinogenicity studies on benzophenones are available". Only studies on Benzophenone-3 were recently finalized by the NTP.

Cosmetic Use – As there is more than one ingredient in this report, please correct "this ingredient" to "these ingredients".

Cosmetic Use; Summary – It is incorrect to report the highest use concentration of Benzophenone-4 in 1983 as ≤10%. The concentration range was 5-10%.

ADME, Human, Dermal – Reference 49 is a biomonitoring study and should be moved to the Biomonitoring section.

The estimated exposure calculations from reference 52 do not belong in the ADME section.

Short-Term, Oral – Please indicate if the 90-day oral study in rats (reference 6) was a dietary or drinking water study.

DART, Embryo/Ovary Cultures – Were DMSO controls included in references 73 and 74?

Genotoxicity, In Vivo, old report summary – It states: “Chinese hamster bone marrow cells from animals (species not stated)”. The species is stated: “Chinese hamster”.

Genotoxicity, In Vivo – Units of mg/kg bw should be called doses rather than concentrations (reference 88).

Tumor Promotion – It is not clear what is meant by "standard dose" or "0.1 dose" as the doses are stated as 0.7, 7, and 70 mg/kg bw.

Effect on Gene Expression – It is unlikely that the offspring were exposed to Benzophenone-3 through milk after weaning.

Other Clinical Reports; Summary – All the studies in this section (except the last study) are epidemiology studies not clinical reports and should be moved to the Epidemiology section. The last study should be moved with the other phototoxicity/photosensitization studies.

Risk Assessment – Please state the source of the 200 mg/kg NOAEL.

The dermal penetration study should be in the Dermal Penetration section.

Summary – “in vitro” is not necessary when describing a zebrafish embryo study

Please revise: “used to evaluated the genotoxicity”

Please correct “TP” to “NTP” and “D” to “GD”

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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: March 9, 2021

SUBJECT: Draft Tentative Report: Safety Assessment of Diacetone Alcohol as Used in Cosmetics (draft prepared for the March 11-12, 2021 meeting of the Expert Panel for Cosmetic Ingredient Safety)

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

Key Issues

Impurities – In the Composition section of the ECHA dossier, it states that the degree of purity of Diacetone alcohol is ≥99% -100% w/w. Although an amount is not stated, they also list acetone as an impurity.

The safety studies cited to the ECHA dossier should be checked to see if they state the purity of the material tested. For example, the 001 Key genotoxicity study (bacterial reverse mutation assay) states that the material tested was 99.8% pure. This information should be added to the CIR report.

A random check of the ECHA dossier indicated that some studies in the dossier are not included in the CIR report. For example reference 2 in the ADME section of the ECHA is described as follows: "This study was performed to obtain blood samples from rats at selected time points following a single 6-hour exposure of the test atmosphere of Diacetone Alcohol at two different concentration levels of Low (500 ppm) and High (1000 ppm) in order to determine the concentrations and the pharmacokinetics parameters of Diacetone alcohol (DAA), Methyl-isobutyl ketone (MIBK) and Methylisobutylcarbinol (MIBC) from the plasma." There is also a second guinea pig maximization study (study date 1978) in the ECHA dossier.

Additional Considerations

Definition and Structure – The Log K_{ow} should be presented in the Chemical Properties section rather than the Definition and Structure section.

ADME – Please state the analytical method used in the oral ADME study.

Acute; Summary – The statement "The lowest LD_{50}s reported for mice, rats, and rabbits were…" implies that there was more than one study completed for each species. Although this is true for rats, there was only one study in mice, and only one study in rabbits so the values stated are the only LD_{50}s in mice and rabbits.

Subchronic, Inhalation – The analytical concentration as provided in the ECHA dossier should also be stated in the CIR report: "analytical concentrations of 0, 233, 1041 and 4685 mg/m^3".

Dermal Irritation, Animal – Please revise: "no irritation was performed"

Dermal Irritation, Human – Please revise: "on the back on the hands" (second "on" should be "of")

Summary – Please clarify "low magnitude"

Please state the system used for the chromosome assay.

When describing the guinea pig maximization test, the injection induction concentration should also be stated.

Please revise: "to observed potential eye irritation"

Draft Discussion – As there are no chronic studies in the CIR report, "chronic" should be revised to "subchronic".

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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: March 8, 2021

SUBJECT: Draft Report: Safety Assessment of Acryloyloxyethyl Phosphorylcholine Polymers as Used in Cosmetics (draft prepared for the March 11-12, 2021 meeting of the Expert Panel for Cosmetic Ingredient Safety)

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

When the information in a section is only about poly(2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate), it is misleading to use Polyquaternium-51 as the subheading. The subheading should indicate that a read-across compound is being used.

Please see the information sheet at https://www.nofamerica.com/store/images/companies/1/images/categories/olo/NOF_Lipidure%20PMB.pdf that indicates that the MW of Polyquaternium-51 is 600K. This sheet also indicates that Polyquaternium-51 is sold at a concentration of 5% in water.

Cosmetic Use; Summary; Table 2 – The highest use concentration reported in the PCPC survey was 0.18% Acrylic Acid/Phosphorylcholine Glycol Acrylate Crosspolymer in foundations. This contrasts with 0.14% Polyquaternium-51 in face and neck products as stated in the CIR report.

Short-Term, Intraperitoneal – What were the toxicity endpoints that were assessed in reference 13?

Inhibition of Skin Penetration – This study should be presented directly after the skin penetration section.

Tissue Regeneration – It is not clear why "high throughput biochemical assays" are mentioned in the introduction to this section as this type of assay is not used in the studies presented under the Polyquaternium-51 subheading.

Summary – Please revise "Most polymers…" to limit the discussion to the polymers included in this CIR report.

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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: March 8, 2021

SUBJECT: Draft Report: Safety Assessment of *Salvia officinalis* (Sage)-Derived Ingredients as Used in Cosmetics (draft prepared for the March 11-12, 2021 meeting of the Expert Panel for Cosmetic Ingredient Safety)

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

Key Issues

Memo – It is not correct to state that Salvia Officinalis (Sage) Flower/Leaf/Stem Water is an essential oil. Although essential oils and waters are often made by the same process, the oil is the water-insoluble fraction, and the water is the water-soluble fraction. This is some information from the Dictionary description of essential oils and waters: "The most widely used method for preparing Essential Oils from plants is associated with steam distillation. The condensate from steam distillation produces two distinct fractions that contain the volatile ingredients from the plant. The water insoluble fraction contains the "oil." The water soluble fraction contains ingredients from the plant that are water soluble. The name assigned to the water insoluble fraction from steam distilled plant materials is identified by the term "Oil" in the INCI name. The water soluble fraction from the steam distilled plant material is identified by the term "Water" in the INCI name."

Introduction – The ECHA dossier (when checked on 2/18/2021) on the sage material says: "Essential oil of *Salvia officinalis* (Lamiaceae) obtained from leaves, flowers and stalks by steam distillation." Therefore, the following sentence in the Introduction is not correct and needs to be revised. "However, based on the International Union of Pure and Applied Chemistry (IUPAC) definition for this substance in ECHA, these data were deemed to refer to the Salvia Officinalis (Sage) Flower/Leaf/Stem Water ingredient, and have been described as such, when cited in this report." Although the Dictionary did not include the generic CAS number 84082-79-1 with the sage essential oils, it does not mean that it was not appropriate for these ingredients. Joanne Nikitakis checked this generic CAS number and determined that it is also appropriate for the

essential oil ingredients and it has been added to the essential oil ingredients. Note that the ECHA dossier also lists the CAS number 8022-56-8 which is also associated with the essential oils in the Dictionary.

Throughout the report, the information cited to the ECHA dosser (reference 2) should be presented under Salvia Officinalis (Sage) Leaf Oil or Salvia Officinalis (Sage) Oil.

Additional Considerations

Non-Cosmetic Use – As it is unlikely that FDA ever "approved" a drug use for sage oil, please revise: "sage oil may have been approved previously as an active ingredient in over-the-counter, astringent drug products" to "sage oil may have previously been used as an active ingredient….".

DART – The statement: "Both mammary glands were excised…" implies that rats have 2 mammary glands when they have 6 pairs of mammary glands. Did they identify which two mammary glands were excised? Or were they randomly selected.

Summary – The number associated with rinse-off products should be 116 not 213 (which is the total number of products with the leaf extract).

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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: March 8, 2021

SUBJECT: Draft Tentative Report: Safety Assessment of Saccharide Humectants as Used in Cosmetics (draft prepared for the March 11-12, 2021 meeting of the Expert Panel for Cosmetic Ingredient Safety)

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

Key Issues
The MW of the DSM Saccharide Isomerate (120-400 Daltons) needs to be clearly stated in the CIR report.

Because the Saccharide Isomerate ingredients from the two suppliers are very different, the material tested needs to be clearly identified throughout the report.

Additional Considerations
Throughout the report, please change “aqua” to “water”.

Method of Manufacture – The following is not correct as DSM did provide a method of manufacture which is presented under Saccharide Isomerate: “nor were such methods submitted as unpublished data”.

Composition and Impurities – The following is not correct as some information has been provided by industry: “nor were such methods submitted as unpublished data.”

Composition and Impurities, Saccharide Isomerate - This should also state that this supplier indicated that their Saccharide Isomerate is "a mixture of mono and disaccharides, mainly glucose and fructose" Since the MW from the other supplier is stated, the MW of this material should also be stated.

Short-Term and Chronic – In the 28-day study of the mixture containing Anhydroxylitol (reference 3), it would be helpful to also state the low dose.

Short-Term and Chronic; Summary – Should “glycogen disposition” be “glycogen deposition”?

Effects of Epidermal Barrier Recovery – Where there any controls in this study (reference 49)?

Dermal Irritation and Sensitization – The intradermal injection concentrations used in the maximization studies should also be stated in the text.

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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: March 8, 2021

SUBJECT: Draft Final Report: Safety Assessment of *Cocos nucifera* (Coconut)-Derived Ingredients as Used in Cosmetics (draft prepared for the March 11-12, 2021 meeting of the Expert Panel for Cosmetic Ingredient Safety)

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

More information on the composition of coconut sap (nectar) is available in:

Asghar MT, Yusof YA, Mokhtar MN, et al. 2019. Coconut (*Cocos nucifera* L.) sap as a potential source of sugar: Antioxidant and nutritional properties. *Food Science and Nutrition*. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7174220/pdf/FSN3-8-1777.pdf)

Composition/Impurities, Liquid Endosperm – Is “dihydroxyphenylaline” correct? Or should this be “dihydroxyphenylalanine”?

Summary – Please revise: “was administered orally to male mice extract”

Please revise: “concentrations of crude ranging from”

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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: March 8, 2021

SUBJECT: Draft Final Report: Safety Assessment of *Carica papaya* (Papaya)-Derived Ingredients as Used in Cosmetics (draft prepared for the March 11-12, 2021 meeting of the Expert Panel for Cosmetic Ingredient Safety)

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

Key Issue
DART – In the following sentence, please change "fruit extract" to "leaf extract": "In a different study, male rats were given 100, 200, or 400 mg/kg bw of a methanolic *Carica papaya* fruit extract via gavage for 28 d." This would be consistent with the title of reference 42 and the information presented on this study in Table 7.

Additional Considerations
Chemical Properties – It should also be stated that the UV absorption spectrum was completed on a 1% dilution of the test material.

Method of Manufacturing, Carica Papaya (Papaya) Fruit Water – Please add the word "steam" before distillation.

Cosmetic Use; Summary – To be consistent with the PCPC use survey, please state the specific FDA product categories in which the highest use concentrations were reported
.
Acute; Short-Term and Chronic – The title of reference 41 indicates that an aqueous fruit extract was studied. Please add "aqueous" when describing this fruit extract.

Summary – The recently provided UV spectrum should be mentioned in the Summary.

The plant part (leaf) should be added to this sentence: "In a different study, male rats were given 100, 200, or 400 mg/kg bw of a methanolic *Carica papaya* extract via gavage for 28 d."

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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: March 9, 2021

SUBJECT: Draft Tentative Amended Report: Safety Assessment of Silicates as Used in Cosmetics (draft prepared for the March 11-12, 2021 meeting of the Expert Panel for Cosmetic Ingredient Safety)

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

Key Issue
Table 3 – Information on crystallinity and purity presented in references 17 and 18 are not included in this table. Reference 17 indicated that Magnesium Aluminum Silicate was 100% pure and that “"Four discrete lots of product were tested for the presence of crystalline silica. In each case, the result was non-detectable (limit of detection = 0.1%).” Reference 18 indicated that Sodium Magnesium Silicate was 100% pure, and regarding crystalline silica; none was detected by XRD qualitative analysis. This information needs to be added to Table 3.

Additional Considerations
Definition; Discussion – The additional information provided by suppliers indicates that ingredients sourced from mined materials can also contain levels of crystalline silica below detection. Therefore, the source of the ingredient is not as significant as implied in the Definition and Discussion sections.

Non-Cosmetic Use, Sodium Magnesium Aluminum Silicate – “paper filer” should be corrected to “paper filler” (see https://bioresources.cnr.ncsu.edu/resources/fillers-for-papermaking-a-review-of-their-properties-usage-practices-and-their-mechanistic-role/ for information on paper fillers)

Summary - The California REL should not be described as an “occupational exposure value”. It is "designed to address continuous exposures for up to a lifetime: the exposure metric used is the annual average exposure"

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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: March 9, 2021

SUBJECT: Draft Tentative Report: Safety Assessment of Red Algae-Derived Ingredients as Used in Cosmetics (draft prepared for the March 11-12, 2021 meeting of the Expert Panel for Cosmetic Ingredient Safety)

The Personal Care Products Council respectfully submits the following comments on the draft tentative report, Safety Assessment of Red Algae-Derived Ingredients as Used in Cosmetics.

Algae Identification – In this section, it would be helpful to discuss the species of red algae that have calcium deposits in their cells, e.g., *Corallina officinalis* and *Lithothamnion calcareum*.

Rhodophyta is a phylum not a family.

Based on this NOAA website https://oceanservice.noaa.gov/facts/redtide.html , scientists are using the term "harmful algae blooms" instead of red tide. Please revise: "that produce the red tidal blooms known as "red tide"" to: "that produce the harmful algae blooms known as "red tide"."

Composition/Impurities, Gelidium Sesquipedale Extract – Rather than saying "Ashes …. were detected in amounts of 0.4 g/100 g", it would be better to state mineral matter, or incombustible matter. Ashes are not actually in the extract; it is what is left after the extract is burned.

Composition/Impurities, Palmaria Palmata – It would be helpful to state the significance of the presence of kainic acid. Since a *Digenia simplex*-derived ingredient is included in the report please add a subsection for this species. Additional composition information on this species is found in the following reference:

Alwaleed EA. 2019. Biochemical composition and nutraceutical perspectives Red Sea seaweeds. *American Journal of Applied Sciences*. 16(12): 346-354. DOI: 10.3844/ajassp.2019.346.354 (at: ajassp.2019.346.354.pdf (thescipub.com))

Composition/Impurities, Gigartina Stellata Extract and Corallina Officinalis Extract - Kappaphycus Alvarezii Extract also needs to be added to this subheading as it is now included in the CIR report.

Cosmetic Use – Please add “used” to “in formulations that are near the eye”

Subchronic – Were the “differences” in organ weights increases or decreases? Which organs were affected?

Irritation – The product containing Delesseria Sanguinea Extract was tested as described (undiluted).

Sensitization; Summary; Table 14 – It should be made clear that the product containing 2% Corallina Officinalis Extract was a blusher that was moistened with water so that it would stick to the skin (reference 77). This is a typical method for testing powder products. It is misleading to state that this product was diluted (as stated in the report memo the Summary and Table 14).

Summary – Some information on the variable composition of these ingredients should be stated in the Summary.

It should be made clear that reproductive toxicity in rats was only studied on gestation days 1-8. The statement “at different stages of gestation” suggests the rats were also exposed in later stages of gestation.

Please correct “No irritation as reported” to “No irritation was reported”

Discussion – The Discussion should state why the Expert Panel is concerned about kainic acid.

[For Pearce 2019 the full paper is not included to protect copyright, but the citation is as follows:]

K. Pearce, W.T. Goldsmith, R. Greenwald, C. Yang, G. Mainelis & C. Wright (2019) Characterization of an aerosol generation system to assess inhalation risks of aerosolized nano-enabled consumer products, Inhalation Toxicology, 31:9-10, 357-367, DOI: 10.1080/08958378.2019.1685613 To link to this article: https://doi.org/10.1080/08958378.2019.1685613