

Wave 2 Data Supplement

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EXPERT PANEL MEETING

SEPTEMBER 11-12, 2023



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, Senior Scientific Analyst/Writer, CIR
Jinqiu Zhu, PhD, DABT, ERT, DCST, CIR Toxicologist
Date: August 31, 2023
Subject: Wave 2 - Response to WVE's comments on Charcoal ingredients

The enclosed comments received from Women's Voices for the Earth (WVE), dated August 28, 2023, on the draft report of charcoal ingredients are submitted for the Panel's review in this Wave 2 submission.

In their comments, WVE expressed concern that there may be potential confusion between the ingredients activated charcoal, Charcoal Powder, and carbon black, as all 3 may be associated with a generic CAS No., i.e., 7440-44-0. However, the generic nature of many CAS Nos. does not mean that the multiple chemicals assigned to one number are the same, or even closely related. In the *Dictionary*, Charcoal Powder is also associated with CAS No. 16291-96-6 and carbon black (an approved colorant) is also associated with CAS No. 1333-86-4; activated charcoal is not currently listed in the *Dictionary*. Both the *Dictionary* and communications with the International Nomenclature Committee (INC) indicate that the source material for the cosmetic ingredients Charcoal, Charcoal Powder, and Charcoal Extract is plant-based, while carbon black is sourced from minerals (e.g., petroleum). Clarification on the ingredient source for activated charcoal is being sought; however, the data in the report indicate it is also sourced from plants (bamboo). While there may be overlap on the CAS No., which is *not* a vetted and unique identifier, these ingredients are not the same. Carbon black and ingredients derived from Charcoal are not produced in the same manner (i.e., sourced from petroleum or plants, respectively) and are likely to have different compositions and impurities. The data in the report are specific to the plant-based materials and do not include carbon black.

Regarding WVE's concerns for the possible use of charcoal powder in dry shampoos, in current regulatory context, dry shampoo has not yet been defined by regulatory agencies. Broad market research indicates dry shampoo may come in various forms, including aerosol sprays, foams, and powders. Dry shampoo foam may be associated with fewer inhalation safety concerns. However, a recent study showed that dry shampoos (powder, packaged in propellant-based sprays) released the highest percentage of respirable droplets/particles (16.66 - 32.27%).¹ The Panel noted these data at the June 2023 meeting, during the review of phenyl-substituted methicones, and determined that "*the available data are insufficient to make a determination of safety for these ingredients in products that may be incidentally inhaled.*"

Meanwhile, it should be noted that, in August 2023, the US FDA Office of Cosmetics and Colors distributed for comment the *Draft Guidance for Industry: Registration and Listing of Cosmetic Product Facilities and Products*. (It has been submitted to the Panel at this current meeting.) However, the new proposed categories still do not cover dry shampoo; hair sprays and hair shampoos are listed separately as subcategories under Hair Preparations Category. Feedback concerning the classification of dry shampoo, along with other issues pertinent to inhalation safety assessment, will be forwarded to the FDA by CIR. (Similarly, WVE is anticipated to directly submit their own observations and queries to the FDA for additional clarification on exposure metrics associated with dry shampoo usage.)

The Panel is requested to review these comments and consider whether there is a need to discuss carbon black in the report. Additionally, the Panel is requested to guide the discussion on the safety concerns associated with possible use of charcoal powder in dry shampoos.

¹Berrada-Gomez MP, Bui B, Bondarenko H, Ferret PJ. Particle size distribution in the evaluation of the inhalation toxicity of cosmetic spray products. *Regul Toxicol Pharmacol.* 2023;139:105359.



August 28, 2023

To the CIR:

I am writing to provide comments on the draft Safety Assessment of Charcoal Ingredients as Used in Cosmetics.

1) A discussion of related ingredient carbon black is needed in this safety assessment.

I noted in the draft that there is no discussion of “carbon black” in the draft. However, unfortunately, there is considerable overlap/confusion in the literature and in the industry between the terms “Charcoal powder”, “Activated Charcoal” and “Carbon black”. The CIR safety assessment should better clarify which substances are included (or not) to avoid confusion on the part of manufacturers using similar substances in their cosmetics.

Carbon black, is both an IARC and Proposition 65 carcinogen, with considerable concern for particles of respirable size. This information is not currently mentioned in the CIR assessment. It appears carbon black would be an inappropriate ingredient for cosmetics -particularly for cosmetics that could be inhaled.

In the CIR draft assessment, charcoal powder, is referred to by the CAS #s 7440-44-0 and 16291-96-6.

The CAS# 7440-44-0 however is also used occasionally by other entities to identify the ingredient “carbon black”.

- a) The National Institutes of Health (NIH) PubChem database for instance, includes an entry on Activated Charcoal - found here:

<https://pubchem.ncbi.nlm.nih.gov/compound/carbon>

This entry lists 7440-44-0 as one of the CAS #s for activated charcoal, but also refers to the substance as “carbon black” throughout. Accordingly, the NIH chose to include information about the carcinogenicity of carbon black, and its inclusion on the IARC carcinogen list, in their Pub Chem summary on Activated Charcoal.

The Consumer Products Ingredient Database (created by the Household & Commercial Products Association HCPA) also lists the INCI name “Carbon Black” with CAS# 7440-44-0 on their entry for “carbon black dispersion”. (Many ingredient supplier members of HCPA are also members of PCPC, so nomenclature consistency is important.)

<https://www.productingredients.com/ingredient/info/carbon-black-dispersion>

Not surprisingly, some cosmetic ingredient suppliers also associate the ingredient name carbon black with the CAS # 7440-44-0.

The supplier website Specialchem.com lists cosmetic colorant CI 77266 by the IUPAC name “carbon black” and lists 7440-44-0 as one of the CAS #s.

<https://cosmetics.specialchem.com/inci-ingredients/ci-77266>

As a result, one can also find “carbon black” listed on Safety Data Sheets of cosmetic products identified by the CAS # 7440-44-0. For example:

<https://store.facepaint.com/pdf/Kryvaline/80265%20%28FS-10R%29%20%20ITA%2017738-%20TWNH00032476%20updated%2028112013.pdf?dl=0>

The CIR Safety Assessment of Charcoal Ingredients as Used in Cosmetics should acknowledge this common association of the ingredient carbon black with the CAS# 7440-44-0. The assessment should also either add “carbon black” as a relevant and related ingredient to the assessment, or explicitly clarify and explain why this assessment does not include the ingredient “carbon black”.

It is important to clarify this, so that the CIR assessment would not lead a cosmetics manufacturer to misunderstand the potential hazards (such as carcinogenicity) of an ingredient (sold to them as CAS# 7440-44-0, but which is in fact carbon black.)

2.) Charcoal powder is also an ingredient in some dry shampoos, which have greater risk of inhalation than many other cosmetic products.

As mentioned in my previous comments on Methicones (from May 2023), a recent study found that in propellant (aerosol) sprays an average of 15% of particles emitted were respirable, and of greatest concern were the category of aerosol dry shampoo sprays for which, on average, 25% of particles emitted would be small enough to be deeply inhaled into the lungs.

Source: Berrada-Gomez MP, Bui B, Bondarenko H, Ferret PJ. Particle size distribution in the evaluation of the inhalation toxicity of cosmetic spray products. Regul Toxicol Pharmacol. 2023 Mar;139:105359.
<https://pubmed.ncbi.nlm.nih.gov/36805297/>

It is important to note that charcoal ingredients are also commonly incorporated into dry shampoo products. The current draft however, states:

“In practice, as stated in the Panel’s respiratory exposure resource document (<https://www.cir-safety.org/cir-findings>), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.”

This statement is inaccurate with respect to some cosmetic sprays – in particular dry shampoo sprays, and should be updated.

Dry shampoo products containing charcoal powder:

OGX Purifying + Charcoal Detox Dry Shampoo Spray. (OGX is owned by PCPC member Johnson & Johnson)

<https://www.amazon.com/OGX-Purifying-Charcoal-Activated-Second-Day/dp/B07X8Y8YV5>

“Active cleansing **activated charcoal** and kaolin clay blend help cleanse and purify to promote a clean, healthy scalp.”

HASK Charcoal Purifying Dry Shampoo

<https://haskbeauty.com/products/hair/charcoal-with-citrus-oil/charcoal-purifying-dry-shampoo>

Ingredients: Butane, Propane, Alcohol denat., Oryza sativa (rice) starch, **Charcoal powder***, Citrus grandis (grapefruit) peel oil, Citrus limon (lemon) peel oil, Distardimonium hectorite, Isobutane, Parfum/Fragrance, Citral, Geraniol, Hexyl cinnamal, Limonene, Linalool (***Activated Charcoal/Charbon actif**)

IGK First Class Dry Shampoo Charcoal Detox Dry Shampoo

<https://www.igkhair.com/products/first-class-charcoal-detox-dry-shampoo?variant=40357990006828>

“This heavy-duty charcoal dry shampoo allows you to go even longer between washes, even after workouts. **Detoxifying charcoal powder** lifts dirt and build up while absorbing oil and sweat.”

My Hair. My Canvas. Another Day dry shampoo

<https://alternahaircare.com/products/my-hair-my-canvas-another-day-natural-dry-shampoo>

Isobutane, Alcohol Denat. (SD Alcohol 40-B), Dimethylimidazolidinone Rice Starch, Zeolite, Aqua/Water/EAU, C12-15 Alkyl Benzoate, Trisiloxane, Parfum/Fragrance, Cetrimonium Chloride, Trimethylsiloxymodimethicone, Benzyl Salicylate, C11-15 Pareth-7, Glycerin, C12-16 Pareth-9, Trideceth-12, Linalool, Citronellol, Limonene, Phenoxyethanol, **Charcoal Powder**, Polysilicone-15, Phospholipids, Caulerpa Lentillifera Extract, Helianthus Annuus (Sunflower) Seed Oil, Sodium Benzoate, Citric Acid.

MANE Club Let's Cheat Charcoal Volumizing Dry Shampoo

<https://www.maneclubnyc.com/products/lets-cheat-dry-shampoo>

INGREDIENTS: Butane, Propane, Alcohol denat., Oryza sativa (rice) starch, Charcoal powder, Citronellyl methylcrotonate, Distearidimonium hectorite, Isobutane, Parfum/Fragrance, Hexyl cinnamal, Linalool

Thank you for your consideration of these comments.

A handwritten signature in black ink on a light-colored background. The signature is written in a cursive style and reads "Alexandra Scranton".

Alexandra Scranton
Director of Science and Research Women's Voices for the Earth



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Jinqiu Zhu, PhD, DABT, ERT, DCST, CIR Toxicologist
Date: August 31, 2023
Subject: Council Comments on the Draft Revised Hair Dye Epidemiology Document

Enclosed are the Council's comments on the Draft Revised Hair Dye Epidemiology Document. Some of the comments are editorial and some related to suggested modifications in preparation for publication. The Council has asked for an appropriate title for the paper for use in submission to an epidemiology journal. And in line with two Panel members suggestions, the Council has requested deleting the only study under Pediatric Germ Cell Tumors section.

Additionally, the Council recommended providing a synthesis of the results in the main body of the text, rather than merely enumerating studies. For example, when summarizing hematologic cancer studies, the text currently lists 19 studies, including 8 meta-analyses. When it comes to aggregating findings (i.e., presenting a synthesis of results) from multiple meta-analysis studies, the Council proposes that a more effective approach is to perform an additional meta-analysis.

If the Panel agrees with this, a previously retained consultant (Dr. Naldi) further proposes that this should be overseen by a trained epidemiologist and should encompass the whole range of available studies, taking care to avoid duplicate data. Sensitivity analysis is also proposed to be utilized to evaluate the impact of including or excluding specific studies.

The Panel is requested to consider the Council comments and provide direction on how to proceed.



Memorandum

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

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

DATE: August 29, 2023

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

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

What is the suggested title of this paper if it is submitted to an epidemiology journal?

Background – If this paper is submitted to a journal, there should be a footnote with the Expert Panel for Cosmetic Ingredient Safety that describes the Panel and CIR and provides links to the CIR and Panel’s websites.

Background - Rather than calling this document a “study” it should be called a “review”.

Background – It should be made clear that references 4 and 12 are also reviews of data not independent studies of cancer incidence among hairdressers.

Background – For submission to a journal, a paragraph on how studies were identified and chosen for inclusion, e.g., only English language studies were included, in this review would be helpful.

Study Summaries – For a publication, it would be helpful if there was more synthesis of the results rather than just a listing of studies in the text as is done in the tables. This is especially true for the cancer types for which there are many studies available.

Breast Cancer – In the description of the WCHS study (reference 37), it says that “recruitment in NJ finished between 2006 to 2014”. The use of the word “finished” is confusing. It would be clearer to state that women were recruited for the study between 2006 and 2014.

Hematologic Cancer – In the description of reference 44 in the hematologic cancer section it mentions results for bladder cancer.

Hematologic Cancer – In the description of the meta-analysis (reference 28) it states: “the results of intensive exposure did not show any association between hair dyes exposure and hematopoietic cancers...”. It is not clear what is meant by “intensive exposure”.

Hematologic Cancer – In the description of reference 54, it is not necessary to restate the reason why an analysis of hair dye use before and after 1980 was completed, as this was stated in the Background section.

Pediatric Germ Cell Tumors – Unless there is more information on how PFHxS is related to hair dye exposure, this study (reference 74) should be deleted from the document.

Genetic Polymorphisms – Since reference 77 is not about the association of hair dyes and cancer, does it belong in this review? If it is left in the review, it would be helpful to note if the Arg/Arg genotype plus hair product exposure (includes more than hair dyes) is associated with an increase in benign breast disease.



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Jinqiu Zhu, PhD, DABT, ERT, DCST, CIR Toxicologist
Date: August 31, 2023
Subject: Wave 2 - CIR SSC Comments on Nitrosation Resource Document

On August 18, 2023, the CIR Science and Support Committee (SSC) of the Personal Care Products Council provided feedback on the draft Nitrosation Resource document. This document was first reviewed by the Panel at the June 2023 meeting.

The CIR SSC recommended a restructuring of the document to include clearer, segmented sections with subheadings. They underscored the importance of addressing potential nitrosation associated with secondary amines during the production or storage of cosmetics and personal care products. In addition, detailed comments have been made for each section of the document, concerning reference selection, data refinement, editorial modifications, structural reorganization, regulatory clarifications, and so forth.

As CIR staff is working with Dr. Ron Shank to revise the Nitrosation Resource document, a comprehensive response to the CIR SSC's comments will be provided along with the revised document in December. ***The Panel is requested to consider these comments, in conjunction with the FDA's guidance on Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities presented at this meeting, and offer further insights and suggestions for the refinement of the Nitrosation Resource document as necessary.***



TO: Bart Heldreth Ph.D., Executive Director – Cosmetic Ingredient Review
Expert Panel for Cosmetic Ingredient Safety

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: August 18, 2023

SUBJECT: Nitrosation Resource Document

The CIR Science and Support Committee (CIR SSC) appreciates the opportunity to comment on the June 2023 draft of the Nitrosation Resource document. As this is an important document, we will also want the opportunity to comment on all future drafts of this document.

The potential for nitrosation is an issue the cosmetics industry has been aware of and managing for many years. Secondary amines should be the focus for cosmetic products as nitrosamines formed from secondary amines are commonly stable compounds. Nitrosamines of secondary amines can be introduced to a finished product as a raw material impurity or formed during manufacturing or storage of the finish product under certain defined conditions. We understand that it is a small subset of ingredients and products, that are of special concern and not a wide ranging concern for cosmetic products.

Rather than trying to cover nitrosation in general, this document should focus on potential nitrosation in cosmetic and personal care products. To make the document more readable, we suggest that it be restructured into shorter sections as follow:

1. What is a nitrosamine
2. Toxicology of nitrosamines
3. Regulations – Cosmetics
4. Nitrosatable species (primary versus secondary, versus tertiary amines; amides, etc.)
5. Nitrosating agents – provide perspective on which are relevant in cosmetics (nitrite, but not nitrosyl halides)
6. Rates of reaction, e.g., pKa of amines
7. Nitrosation accelerators, e.g., aldehydes
8. Nitrosation inhibitors, e.g., antioxidants
9. Methods for measurement, e.g., LC-MS/MS or GC-MS/MS as the preferred techniques, reference ISO 15819 (NDELA)
10. Strategies to minimize nitrosamines in cosmetics (reference to Cosmetic Europe Guidance and ISO 14735)

The Cosmetics Europe 2009 technical guidance document should be used to help focus the CIR resource document.

The following are specific comments on the draft reviewed by the Expert Panel for Cosmetic Ingredient Safety during the June 12-13, 2023 meeting.

Background

The discussion of Nitrosation of amines should be expanded. Primary amines do not form stable nitrosamines. Most tertiary amines nitrosate very slowly and are not generally a concern for cosmetics. Secondary amines should be the focus area for cosmetic products because these are stable compounds. N-Nitrosamines of secondary amines can be introduced into a finished product as a raw material impurity or formed during manufacture or storage of the finished product.

Nitrosation of amides is very slow because the lone pair of electrons on the nitrogen are associated with the carbonyl group of the amide. Primary amides are not stable and will degrade. Secondary amides can nitrosate but require strong nitrosating agents and the reaction is slow. Overall, nitrosation of amides is not considered a problem for cosmetic products, although there is potential for amides to contain amine impurities.

As stated above, the focus of the document should be the formation of N-nitrosamines in cosmetics, which should be made clear from the beginning of the document. Historically, the focus has been on diethanolamine in cosmetics and the possible formation of N-nitrosodiethanolamine (NDELA). In 2011, the SCCS indicated that mainly two nitrosamines (NDELA and N-nitrosobis(2-hydroxypropyl)amine (NBHPA)) have been found in cosmetics. A short list of nitrosamines have ever been found in cosmetics (N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitrosomorpholine (NMOR), N-nitrosopyrrolidine (NPYR), NBHPA, NDELA, and N-nitrosopara-aminobenzoic acid (NPABA)).

Factors influencing the N-nitrosation of ingredients in cosmetic products

This section covers a lot of information, some of which is repeated from the background section. As discussed above, splitting the report into shorter sections would help to make the document more readable.

While the list of nitrosating agents presented in this section is correct, some are not relevant to cosmetic products.

It should be noted that 2-Bromo-2-Nitropropane-1,3-Diol (Bronopol) has two roles in nitrosation. The nitro group provides the nitrosating agent and the formaldehyde catalyzes the reaction.

This section should not mention the “European Cosmetics Directive” as this was replaced by the “Cosmetics Regulation” in 2009.

Information about controlling N-nitrosamines in pharmaceuticals should be moved to the regulatory section.

The document states that “N-Nitrosamines can be quantitatively detected down to 1 ppb.” This statement is too general because the exact limit of quantification (LOQ) will depend on the specific nitrosamine, analytical method used, and the sample matrix.

Current regulations on nitrosamine formation in cosmetic ingredients and cosmetic formulations

The first part of this section is a review of a publication and does not concern regulations. It should be moved to the background section.

We are especially concerned with the section below (in italics) and reference 32. The reported data are not consistent with the surveillance conducted by the German authorities (Annex III of SCCS/1486/12) or reference 34. Since not all cosmetics have nitrosamine impurities and those that have tested positive can have a wide range in values, it does not make sense to list the results from one study that evaluates data as far back as the 1970s and 1980s. Of importance, reference 34 used a validated analytical method and found 13 of 103 cosmetic products in Korea and 4 of 12 raw materials in which NDELA was detected. The range found was from trace (<20 µg/kg) to 214.2 µg/kg. It is also important to indicate that there are a wide range of consumer exposure characteristics that are important when discussing risk (i.e., rinse-off versus leave-on, applied to hair or applied to skin, etc.)

“Contamination of cosmetic products with NDELA is attributed to the interaction of di- or triethanolamine (DEA and TEA, respectively), commonly used ingredients in cosmetics, with a nitrosating agent.^{32,34} The remaining 1% of observed contamination comes from N-nitrosomorpholine (NMOR, ~ 0.99%) and N-nitrosodimethylamine (NDMA, ~ 0.01%). Hair care products (total N-nitrosamine: 1900 ± 1900 ng/g (average ± standard deviation), similarly hereinafter), shampoos (220 ± 50 ng/g), and lotions (100 ± 25 ng/g) all showed quantifiable N-nitrosamine concentrations, with NDELA being the major congener in all cases. Among identified exposure sources through literature review (n = 6), average total N-nitrosamine concentration in cosmetic products ranges from 400 to 49,000 ng/g.”

This section should include a table summarizing regulations, including the FDA drug regulations/guidelines.

The following sentence should be deleted as it does not add useful information and it is contradicted by the descriptions of the regulations that follow: *“While regulatory oversight could significantly reduce daily N-nitrosamine exposure, regulating N-nitrosamines in personal care products would be challenging due to the aforementioned attenuations of carcinogenicity or rates of nitrosation, and numerous existing laws and regulations governing the manufacturing and sale of cosmetics and personal care products.”*

The SCCS section needs to be re-written for clarity. Begin with the regulations in the Annexes of Directive 76/768/EEC which include purity specification of 50 ppb N-nitrosamines for raw materials and all nitrosamines potentially formed. Secondary amine content in raw materials should be as low as achievable and not exceed 5% in raw materials. In finished cosmetic products, a maximum secondary amine content of 0.5% should be maintained.

The 160 ppb value is not an estimated safety level. It is the maximum level of NDELA in finished cosmetic products applied topically that would pose a minimal health risk to the consumer. This assessment was completed by Cosmetics Europe, not by SCCS. The details about the conservative deterministic aggregate exposure assumption should also be detailed in this document.

A T25 value is mentioned, but no number is provided. What is the number?

More details on how the risk assessment was done and all the assumptions used should be included in the text. As written, this does not read well, and is not sufficient. For risk assessments, descriptions of the point of departure, the threshold safety value, exposure assumptions, etc. all need to be described.

If kept in the document, the following, with the indicated revision, should be in the Background section: *“N-Nitrosation may occur in trace concentrations in diverse environments, including air, soil, water, stored or preserved foods, and the gastrointestinal tract of both animals and humans.³⁸ N-Nitrosamine impurities may show up in a variety of cosmetic ingredients. For instance, surfactants and emulsifiers, which are ammonia or amine salts, may serve as potential source of N-nitrosamines. Raw materials based on secondary amines, such as DEA, have the highest potential for N-nitrosamine formation. N-Nitrosamine levels in certain cosmetics may increase over the months following product opening.³⁹ Although ~~commonly present~~ **trace nitrosamines could be present** as contaminants in cosmetic products containing primary, secondary, and tertiary alkyl amines, N-nitrosamines are not listed on product labels since they are impurities or formed by reactions of chemical mixtures in products.”*

Reference 16 is guideline for drug products only. The CIR document indicates that is also for food and cosmetics. This is not correct.

Reference 41 is for the drug, metformin, not for foods.

VSD is incorrectly defined as “Valuable Safety Dose”. It should be “Virtually Safe Dose”. It is customarily a risk level of 1 in 1,000,000. For Proposition 65, the state of California uses 1 in 100,000.

Please provide a reference for FDA guidance on minimizing the formation of nitrosamines during the manufacture of cosmetics. Reference 40 does not include FDA guidance on nitrosamines in cosmetics.

Has FDA issued guidance to manufacturers on preventing N-nitrosamine formation during the manufacture of cosmetics? If so, please provide the reference.

The following sentences should be deleted. Nitrosamines are not intentionally added and will not be included in product labels. *“The US Fair Packaging and Labeling Act (FPLA) requires cosmetic manufacturers to label their products with ingredient information and necessary warning statements to assess consumers in making informed decisions.⁴⁵ While the FPLA does not establish specific provisions for N-nitrosamines or N-nitrosation in cosmetics, manufacturers must comply with labeling requirements if these substances are present and could potentially pose health risks.”*

Safety aspects considered by the Panel for mitigating N-nitrosation potential in cosmetic formulations

Please add “some” before products, as N-nitrosamines have not been found in all products.

It is not clear why indole rings are being used as an example. A better example may be secondary amines like diethanolamine since this is historically more relevant.

The Expert Panel only evaluates the safety of ingredients. It is not correct to state that they consider the “cosmetic package, or at the point of use”.

Please change “would investigate” to “recommends the manufacturer investigate”

The example of DEA should focus on what was said in regard to the potential for NDELA formation, rather than other mechanisms of cancer that have been attributed to DEA.

In the following, replace “detected in cosmetics” with “detected in cosmetics that contain secondary amines and a nitrosation source”: *“Although the levels of N-nitrosamines detected in cosmetics are usually very low”*

In the last paragraph, it should be made clear that not all cosmetic products are impacted. It is just the small number that contain secondary amines and a nitrosation source.

Unless there is a specific reference that can be cited, the document should not state that FDA has guidance for industry to prevent the formation of N-nitrosamines in cosmetics.

Conclusion

In the first sentence, please qualify the N-nitrosamine exposure by saying “When exposure and duration of exposure are high enough, some N-nitrosamines pose health risk...”



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, M.S., Senior Scientific Analyst/Writer, CIR
Date: August 31, 2023
Subject: Safety Assessment of *Olea europaea* (Olive)-Derived Ingredients as Used in Cosmetics

Enclosed are the Council's comments on the Draft Final Report of the Safety Assessment of *Olea europaea* (Olive)-Derived Ingredients as Used in Cosmetics. Most of the comments are minor edits; however, the Panel should review the language in the Discussion section on the dermal absorption of olive ingredients and discuss if any edits or clarification should be made.



Memorandum

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

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

DATE: August 29, 2023

SUBJECT: Draft Final Report: Safety Assessment of *Olea europaea* (Olive)-Derived Ingredients as Used in Cosmetics (draft prepared for the September 2023 meeting)

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

Key Issue

Discussion – In the Discussion, does the Expert Panel really want to state: “that these ingredients do not readily absorb”? As the CIR report includes no ADME data, what is the basis for this statement?

Additional Considerations

Abstract – To be consistent with the safe ingredients, it would be helpful to include the plant parts after the insufficient data ingredients (i.e., bark, branch, bud, flower, sap, wood).

Dermal Irritation and Sensitization; Summary – Please add the word “pig” to: “in a guinea maximization study”.

Case Reports – Please correct “in at 21-yr-old woman” to “in a 21-yr-old woman”



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc., Senior Scientific Analyst/Writer, CIR
Date: August 31, 2023
Subject: Safety Assessment of Myristoyl Pentapeptide-4, Palmitoyl Pentapeptide-4, and Pentapeptide-4 as Used in Cosmetics

Enclosed is an editorial comment from Council (pertaining to the method of manufacture section) on the Draft Report of the Safety Assessment of Myristoyl Pentapeptide-4, Palmitoyl Pentapeptide-4, and Pentapeptide-4 as Used in Cosmetics. Additionally, an updated data profile outlining the available endpoints in this report by amino acid sequence (lysine-threonine-threonine-lysine-serine (KTTKS) vs. lysine-threonine-serine-lysine-serine (KTSKS)) is provided for the Panel's use (*updateddatapoint_Pentapeptides_Wave2_092023*). This document is intended to provide further context to the data being reviewed.



Memorandum

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

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

DATE: August 29, 2023

SUBJECT: Draft Report: Safety Assessment of Myristoyl Pentapeptide-4,
Palmitoyl Pentapeptide-4, and Pentapeptide-4 as Used in Cosmetics (draft
prepared for the September 2023 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft report, Safety Assessment of Myristoyl Pentapeptide-4, Palmitoyl Pentapeptide-4, and Pentapeptide-4 as Used in Cosmetics.

Method of Manufacture – As the method of manufacture provided by the supplier agrees with the general methods of peptide synthesis, please delete: “and it is unknown whether they are specific to ingredients that are used in cosmetics.” Please consider adding a statement to the CIR report indicating that the general methods are consistent with methods of manufacture provided by suppliers that are described later in the section.

Pentapeptides Data Profile* - September 11-12, 2023 - Writer, Preethi Raj

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization			Ocular Irritation		Clinical Studies		
	Reported Use	Method of Mfg	Impurities	log P/log K _{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/Multicenter	Case Reports
Myristoyl Pentapeptide-4	X																												
Palmitoyl Pentapeptide-4	X																												
• Pal -KTTKS		X	X	X	X				X	X				X					X	X		X	X		X	X			
• Pal-KTSKS		X	X											X					X	X	X		X	X	X	X			
Pentapeptide-4	X																												
• Pal-KTTKS				X	X																								

* "X" indicates that data were available in a category for the ingredient



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc., Senior Scientific Writer/Analyst, CIR
Jinqiu Zhu, PhD, DABT, ERT, DCST, CIR Toxicologist
Date: August 31, 2023
Subject: Wave 2 - Response to WVE's comments on Phenyl-Substituted Methicones; notice of comments received from the Council

The enclosed comments received from Women's Voices for the Earth (WVE), dated August 22, 2023, on the draft final report of phenyl-substituted methicones are submitted for the Panel's review in this Wave 2 submission.

At the June 2023 meeting, the Panel acknowledged the Silicones, Environmental, Health and Safety Center (SEHSC) statement that the data set previously submitted to CIR was representative of Phenyl Trimethicone. However, the Panel was also made aware that these data were submitted under CAS No. 70131-69-0; this CAS No. is no longer associated with Phenyl Trimethicone in the wINCI *Dictionary*. Specifically, in a memo submitted by the Council on April 28, 2023, and provided to the Panel at the June 2023 meeting, the International Nomenclature Committee (INC) declared that CAS No. 70131-69-0 is not applicable to Phenyl Trimethicone.

On August 15, 2023, the SEHSC submitted a letter to CIR which states that "... *the information submitted on Phenyl Trimethicone was for the material associated with CAS RN 70131-69-0. ... the members would like to confirm that the data on CAS RN 70131-69-0, submitted by SEHSC on behalf of its members, is **not** appropriate for the Phenyl Trimethicone report.*" Hence, in response to the data provider's request and to prevent any potential confusion, study results linked to CAS No. 70131-69-0 have been excluded from the draft final report on phenyl-substituted methicones. While there may be overlap of the chemicals linked to the CAS No., which is **not** a vetted and unique identifier, these ingredients are **not** the same.

In their comments, WVE is asking the Panel to reinstate the SEHSC data back into the report, citing a number of sources of information, including safety data sheets, that are linked to CAS No. 70131-69-0. However, while both the SEHSC and the INC have conceded that this CAS No. has been erroneously linked to at least 2 disparate chemicals, the error is of a global nature and not yet corrected elsewhere. Indeed, it seems that the sources of information cited by WVE in this instance are linked to polysilsesquioxanes, and thereby not relevant to the safety assessment of these phenyl-substituted methicones.

Additionally, please note that comments received from the Council are also included herein.



Memorandum

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

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

DATE: August 29, 2023

SUBJECT: Draft Final Report: Safety Assessment of Phenyl-Substituted Methicones as Used in Cosmetics (draft prepared for the September 2023 meeting)

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

Key Issue

The Discussion needs to be revised based on the August 15, 2023 clarifying memo from SEHSC. This memo indicates that the information on the material associated with CAS No. 70131-69-0 (no longer associated with Phenyl Trimethicone in the Dictionary) is not appropriate for this CIR report.

Additional Considerations

Acute – Please add the word “study” to “in an acute oral toxicity evaluating”

DART; Table 6 first study description – Please correct “ration” to “ratio”

August 22, 2023

Re: Comments on the draft Safety Assessment of Phenyl-Substituted Methicones as Used in Cosmetics.

To the CIR Expert Panel:

I noted in the recent Admin memo that the previous data on Phenyl Trimethicone (with the CAS # 70131-69-0) submitted by the SEHSC has been removed from the Draft Final Report. The rationale is the SEHSC's understanding that CAS No. 70131-69-0 is no longer associated in the INCI Dictionary with the INCI name Phenyl Trimethicone, based on a recent re-evaluation of CAS numbers by the International Nomenclature Committee.

We are asking the CIR Expert panel to reinstate the SEHSC data back into the Final Report due to its clear relevance in cosmetics today, and its importance in assessing the safety of the cosmetic ingredients called "Phenyl Trimethicone".

While the INCI committee appears to have determined the CAS #70131-69-0 to be misclassified, it appears, in practice, that chemical manufacturers that manufacture cosmetic ingredients still currently manufacture the substance with the CAS# 70131-69-0 as a cosmetic ingredient – and that they still refer to this substance as "Phenyl Trimethicone" as the INCI name when selling to their customers. Furthermore, there are numerous cosmetic product manufacturers who also include "Phenyl Trimethicone" in their products – and refer to this substance on their safety data sheets as having CAS # 70131-69-0, and in their ingredient listings as "phenyl trimethicone".

Given the still common usage of this substance (identified as CAS# 70131-69-0 and referred to as "Phenyl Trimethicone") by cosmetics manufacturers and chemical manufacturers, it is appropriate to include the SEHSC toxicity data on this substance in the Final Report on Phenyl-substituted Methicones. Further – given that both the term "Phenyl Trimethicone" is (and has been) used to describe chemicals identified by several different CAS #s, the CIR may not be able to discern which chemicals are referred to in much of the research gathered on "Phenyl Trimethicone". The CEHSC does specify CAS#s for their data but other research on Phenyl Trimethicone the CIR is relying on may not. (Unfortunately, virtually all of the research gathered for this report is non-peer-reviewed unpublished data, that is unavailable for outside review.)

As you are aware, the CEHSC inhalation toxicity data associated with CAS# 70131-69-0 was of great concern.

"All rats in the 5.0 mg/L and half of those in the 0.5 mg/L (nominal) exposure group died within 24 hours of exposure."

Given that this ingredient is both used in cosmetic products (including spray products with the potential to be inhaled) and is referred to as "Phenyl Trimethicone" on both SDS sheets and ingredient listings, it is important to include the SEHSC data in your safety assessment of the ingredient by this name. It

would be misleading to omit this data, and issue a “Safe as used” conclusion for “Phenyl Trimethicone” with the details of the limited specific CAS #s the CIR intends this ingredient term to refer to buried deep in the text. This is especially true given your knowledge that both chemical and product manufacturers still commonly use the INCI name “Phenyl Trimethicone” for the substance identified by the CAS # referred to in the SEHSC data.

Both manufacturers and consumers are counting on the CIR to review the safety of all ingredients actually included in products by that name. It would be a disservice to all to omit critical inhalational toxicity data for Phenyl Trimethicone , CAS # 70131-69-0.

It appears from the SEHSC’s recent letter of August 25, 2023 that their members now understand that CAS # 70131-69-0 is no longer associated with the INCI name phenyl trimethicone. However, this does not eliminate the reality that there are cosmetic products currently on the shelves containing the substance CAS # 70131-69-0, and calling that ingredient “Phenyl Trimethicone”. There are also cosmetic ingredient suppliers that are not members of SEHSC that may not be aware of the new INCI determination. Finally, there are certainly products represented in the VCRP data as including Phenyl Trimethicone, that actually contain CAS# 70131-69-0.

Data from Safety Data Sheets (SDS):

I did a google search for the term “SDS Phenyl Trimethicone 70131-69-0”. This search returned safety data sheets from chemical manufacturers for cosmetic chemicals, for cosmetic ingredients which they call the INCI name Phenyl Trimethicone and identify as CAS # 70131-69-0. This same search also returned numerous safety data sheets for cosmetic products (including those manufactured by PCPC members L’oreal, Kao, Henkel etc.) which list Phenyl Trimethicone identified by CAS #70131-69-0 as an ingredient.

For example,

Dow (an SEHSC member) manufactures Dowsil™ 556 Cosmetic Grade Fluid

According to the Technical Data Sheet, the INCI name for this ingredient is “Phenyl Trimethicone”, and its intended applications are as a water repellent additive in lotions and a hair gloss agent in hair products.

<https://www.dow.com/en-us/pdp.dowsil-556-cosmetic-grade-fluid.01010476z.html#tech-content>



Technical Data Sheet

DOWSIL™ 556 Cosmetic Grade Fluid

INCI NAME: Phenyl Trimethicone

Applications

- Used as a water repellent additive and to reduce the tackiness and stickiness of organic ingredients in formulations such as:
 - skin lotions and creams
 - suntan lotions and non-aerosol sprays
 - pre-shave lotions
- Used as a hair gloss agent in non-aerosol hair sprays, conditioners and grooming aids

The Safety Data Sheet for Dowsil 556 Cosmetic Grade Fluid clarifies that this product is composed of 99-100% of the substance with CAS # 70131-69-0, and includes the warning language “Fatal if inhaled”.



SAFETY DATA SHEET

THE DOW CHEMICAL COMPANY

Product name: DOWSIL™ 556 Cosmetic Grade Fluid

Issue Date: 05/03/2021
Print Date: 05/04/2021

3. COMPOSITION/INFORMATION ON INGREDIENTS

Synonyms: Silsesquioxanes, phenyl trimethylsilyloxy-terminated

This product is a substance.

Substance name: Silsesquioxanes, phenyl trimethylsilyloxy-terminated

CASRN: 70131-69-0

Component	CASRN	Concentration
Silsesquioxanes, phenyl trimethylsilyloxy-terminated	70131-69-0	>= 99.0 - <= 100.0 %

Similarly, my google search included three additional suppliers of cosmetic grade Phenyl Trimethicone, **Siltech**, **Kobo** and **Gelest**, which refer to this substance on their safety data sheets by the INCI name Phenyl Trimethicone and identified as CAS # 70131-69-0.

Siltech (PCPC Member) manufactures Siltech PTM.

The technical data sheet for Siltech PTM refers to the INCI name for this product as Phenyl Trimethicone, and includes many of the same cosmetic functions such as high gloss in hair care products, and use in lotions and creams.

<https://www.siltech.com/wp-content/uploads/2023/03/Siltech-PTM-TDS.pdf>

The safety data sheet indicates that Siltech PTM is composed of 90-100% CAS# 70131-69-0, and includes the warning language “Fatal if inhaled.”

https://www.siltech.com/wp-content/uploads/2023/03/SDS-0052.6-Siltech-PTM_GHS.pdf



SAFETY DATA SHEET

WHMIS 2015 • OSHA HCS (29 CFR 1910.1200) • NOM-018-STPS-2015

1. SECTION 1: IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/UNDERTAKING

1.1 Product identifier

Product Name	Siltech PTM
Product code	0052.6
Chemical Name	Silsesquioxanes, Ph
CAS No.	70131-69-0
Alternative names (INCI)	PHENYL TRIMETHICONE

1.2 Recommended use of the chemical and restrictions on use

Identified use(s)	PC39 Cosmetics, personal care products
Uses advised against	None known

Kobo (PCPC Member) also manufactures a cosmetic ingredient called Phenyl Trimethicone, composed of CAS# 70131-69-0.

<https://www.knowde.com/stores/kobo-products/products/kobo-products-cpf-3300-10cst>

Gelest also manufactures a cosmetic ingredient TMS-P13, composed of 95-100% CAS# 70131-69-0, and includes the warning language “Fatal if inhaled.”

https://s3.amazonaws.com/gelest/sds/TMS-P13_GHS+US_English+US.pdf

Cosmetic Products containing Phenyl Trimethicone CAS # 70131-69-0

As for cosmetic products containing this ingredient, my google search of “SDS Phenyl Trimethicone 70131-69-0” found numerous products using this nomenclature and CAS #. Examples (particularly of spray products include:

PCPC Member L’oreal USA Inc. manufactures Pureology Smooth Perfection Smoothing Serum spray which lists “Phenyl Trimethicone CAS # 70131-69-0” as an ingredient:

3. Composition/information on ingredients

Mixtures

Chemical name	Common name and synonyms	CAS number	%
HEXYLENE GLYCOL		107-41-5	8

Material name: PUREOLOGY SMOOTH PERFECTION SMOOTHING SERUM
86093 PUR25 Version #: 01 Issue date: 06-27-2019

SDS US
1 / 7

Chemical name	Common name and synonyms	CAS number	%
PHENYL TRIMETHICONE		70131-69-0	3.5

https://www.maritimebeautyshop.com/images/msds/PLGY_ANTISERUM.PDF

PCPC Member Kao USA Inc. manufactures Goldwell Kerasilk Control Beautifying Hair Perfume spray which lists "Phenyl Trimethicone CAS # 70131-69-0" as an ingredient:

Page 2/8

Safety Data Sheet acc. to OSHA HCS

Printing date 05/16/2017

Reviewed on 05/16/2017

Trade name: GOLDWELL KERASILK CONTROL Beautifying Hair Perfume



· **vPvB:** Not applicable.

(Contd. of page 1)

3 Composition/information on ingredients

- **Chemical characterization: Mixtures**
- **Description:** Mixture of the substances listed below with nonhazardous additions.

· **Dangerous components:**

CAS: 64-17-5	ethanol	 Flam. Liq. 2, H225	50-75%
CAS: 70131-69-0	Phenyltrimethicone	 Acute Tox. 2, H330	0.1-≤2.5%

https://www.goldwell.com/content/dam/sites/kaousa/www-goldwell-com/content/us/en_us/pdf/kerasilk_msds/gw-kerasilk-control-beautifying-hair-perfume-2021.pdf

PCPC Member Henkel manufactures Smooth N Shine Instant Repair Spray on Hair Polisher which lists "CAS # 70131-69-0" as an ingredient:

Safety Data Sheet



Revision Number: 001.0

Issue date: 10/03/2016

1. IDENTIFICATION OF THE SUBSTANCE OR MIXTURE AND OF THE SUPPLIER

Product identifier used on the label: Smooth 'N Shine Instant Repair Spray On Hair Polisher

Recommended use of the chemical and restrictions on use: Hair Treatment, leave-on

3. COMPOSITION / INFORMATION ON INGREDIENTS

The following chemicals are classified as health hazards in accordance with paragraph (d) of § 1910.1200.

Chemical Name*	CAS Number (Unique Identifier)	Concentration
Decamethylcyclopentasiloxane	541-02-6	30 - 60 %
Hydrocarbons, C4, 1,3-butadiene-free, polymd., triisobutylene fraction, hydrogenated	93685-81-5	30 - 60 %
Phenylsilsesquioxanes	70131-69-0	0.1 - 1 %

https://www.whatsinproducts.com/files/brands_pdf/1477060638.pdf

Federici Brands manufactures ColorWow Extra Shine Spray which lists “CAS # 70131-69-0” as an ingredient:

Color Wow Extra Shine Spray

Safety Data Sheet

according to Regulation (EC) No. 1907/2006 (REACH) with its amendment Regulation (EU) 2015/830

SECTION 3: Composition/Information on ingredients			
3.1. Substances			
Not applicable			
3.2. Mixtures			
Name	Product identifier	%	Classification according to Regulation (EC) No. 1272/2008 [CLP]
ethanol, ethyl alcohol	(CAS-No.) 64-17-5 (EC-No.) 200-578-6 (EC Index-No.) 603-002-00-5	30-35	Flam. Liq. 2, H225 Eye Irrit. 2, H319
Hydrofluorocarbon 152A	(CAS-No.) 75-37-6 (EC-No.) 200-866-1	35-40	Not classified
Silsesquioxanes, phenyl trime-	(CAS-No.) 70131-69-0 (EC-No.) 615-071-9	1-5	Acute Tox. 2 (Inhalation:dust,mist), H330

Numerous non-spray cosmetic products also list “Phenyl Trimethicone CAS # 70131-69-0” as an ingredient.

PCPC Member L’oreal USA Inc. manufactures Pureology Colour Stylist Cuticle Polish Shine Serum for Colour-Treated Hair which lists “Phenyl Trimethicone CAS # 70131-69-0” as an ingredient. SDS available at:

https://www.maritimebeautyshop.com/images/msds/PLGY_SHBRTMGSRM.PDF

PCPC Member Kao USA Inc. manufactures KMS Moist Repair Revival Crème which lists “Phenyl Trimethicone CAS # 70131-69-0” as an ingredient. SDS available at:

https://www.kmshair.com/content/dam/sites/kaousa/www-kmshair-com/Master/pdfs/122039_122040_KMS%20MR%20Revival%20Creme.pdf

PCPC Member Kao USA Inc. manufactures KMS Time Frizz Curl Leave-In Conditioner which lists “Phenyl Trimethicone CAS # 70131-69-0” as an ingredient. SDS available at:

https://www.kmshair.com/content/dam/sites/kaousa/www-kmshair-com/Master/pdfs/162039_162040_KMS%20TF%20Curl%20Leave-In%20Conditioner.pdf

Grayson O. Company manufactures Windsor Serum with Argan Oil which lists “Phenyl Trimethicone CAS # 70131-69-0” as an ingredient. SDS available at:

<https://colorvanish.com/wp-content/uploads/2018/05/SDS-Windsor-Serum-with-Argan-Oil-Reversed.pdf>

Hopefully you have have, or will, also hear from PCPC member companies who use the ingredient identified as CAS # 70131-69-0 in their products who will also have a vested interest in your opinion of its safety as used in cosmetic products.

Thanks very much for your consideration of these comments.

A handwritten signature in black ink, reading "Alexandra Scranton". The signature is written in a cursive style with a light grey background behind it.

Alexandra Scranton
Director of Science and Research
Women's Voices for the Earth



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc., Senior Scientific Analyst/Writer, CIR
Date: August 31, 2023
Subject: Safety Assessment of Diglycerin and Polyglycerin-3, -6, and -10 as Used in Cosmetics

Enclosed are the Council's comments on the Draft Final Report of the Safety Assessment of Diglycerin and Polyglycerin-3, -6, and -10 as Used in Cosmetics. Most of the comments are editorial. The Council has requested the Panel to consider adding a statement in the Discussion about these ingredients being large molecules that are not likely to be absorbed in the skin.



Memorandum

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

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

DATE: August 29, 2023

SUBJECT: Draft Final Report: Safety Assessment of Diglycerin and Polyglycerin-3, -6, and -10 as Used in Cosmetics (draft prepared for the September 2023 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft final report, Safety Assessment of Diglycerin and Polyglycerin-3, -6, and -10 as Used in Cosmetics.

Key Issue

Discussion – As the largest compound, Polyglycerin-10 has a MW of 758.8, does the Expert Panel want to state that “these ingredients are large molecules that are not likely to be absorbed in the skin”?

Additional Considerations

Short-Term, Inhalation, Glycerin old report summary – Units of mg/m^3 should be called “concentrations” rather than “doses”. In what media, e.g., serum, was glucose measured?

Subchronic, Oral, Glycerin old report summary – Units of mg/l should be called “concentrations” rather than “doses”.

Dermal Irritation and Sensitization – In the description of the first guinea pig maximization test, please clarify what is meant by “undiluted epicutaneous applications”. Does this mean the 5% aqueous Diglycerin was tested undiluted? Or does this mean Diglycerin was tested undiluted?



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Bart Heldreth, PhD, Executive Director, CIR
Date: August 31, 2023
Subject: Draft Final 2023 Priorities

Enclosed are the Council's comments on the Draft Final 2023 Priorities. There are just 2 comments, both of which are editorial.



Memorandum

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

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

DATE: August 22, 2023

SUBJECT: 2024 Draft CIR Priorities

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

The function for Trimethylbenzoyl Diphenylphosphine Oxide is incorrectly stated as “Hair Colorant”. As stated in the memo, the function should be listed as skin conditioning agent.

As noted in previous PCPC comments, 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.



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, M.S., Senior Scientific Analyst/Writer, CIR
Regina Tucker, M.S., Scientific Analyst/Writer, CIR
Preethi Raj, M.Sc., Senior Scientific Analyst/Writer, CIR
Date: August 31, 2023
Subject: Re-Reviews Wave 2 – Council Comments

Enclosed please find Council’s comments on the following re-review documents:

- Sodium Dehydroacetate and Dehydroacetic Acid
- Isobutane, Butane, Isopentane, and Propane
- *t*-Butyl Alcohol

Sodium Dehydroacetate and Dehydroacetic Acid

It should be noted that the new data document on the re-review of Sodium Dehydroacetate and Dehydroacetic Acid states that an exposure assessment was performed using a 60% maximum concentration. This concentration is incorrect – the maximum concentration used to provide an MOS calculation for Dehydroacetic Acid was 0.6% (Canavez, 2021). In addition, this study also provided an MOS calculation for Sodium Dehydroacetate (61.95), also using a maximum concentration of 0.6%. (This was not previously included in the new data document).

Isobutane, Butane, Isopentane, and Propane

In the new data document on the re-review of Isobutane, Butane, Isopentane, and Propane, in the Dahl et al. 1988 study, it should be noted that 2 rats were exposed one at a time to one of the hydrocarbon vapors. For Isobutane, exposure at 100 ppm was the only available value; the lower two values are means for Isobutane inhaled at 10 ppm.

In the McKee et al 2014 study (Developmental and Reproductive toxicity section), rats were exposed to combination of Isobutane, Butane, and Propane at the same time.

t-Butyl Alcohol

Comment stating that it would be helpful to include concentration in products, in addition to dose.



Memorandum

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

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

DATE: August 29, 2023

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

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

Dehydroacetic Acid and Sodium Dehydroacetate

Zhang et al. 2017, Acute Oral – Please check this study. It appears to be a 13-day study, rather than an acute study. The duration of the study is stated in the legends of the figures. The information with the figures indicates that the rats were treated by “lavage”, which is probably a mistake for “gavage”.

Fang et al. 2023, Repeated Dose – Please state the calculated dose the authors considered to be the benchmark dose.

Registration Dossier, Genotoxicity, In Vivo – Units of mg/kg bw/day should be called “doses” not “concentrations”.

Izawa et al. 2018, Other relevant studies, Photoreactivity – Based on the information provided, it is not possible to determine if this study is relevant. Was this an *in vitro* study? Were the concentrations tested relevant to use of these ingredients in cosmetics?

Canavez et al. 2021, Risk Assessment – More details on how this risk assessment was completed would be helpful. What does the 60% max concentration represent? If this is the maximum concentration in cosmetic products, is it correct? The EU limit is 0.6%. What product types were considered for this risk assessment. Please provide the reference for the study they used as the basis for the NOAEL.

Isobutane, Butane, Isopentane and Propane

Regulation EC No. 1333/2008 is for food additives (cosmetic regulations are found in 1223/2009), so the first row is not for cosmetic use as stated in the table. Annex II (prohibited) of the EU cosmetic regulations lists Butane and Isobutane, but only if they contain $\geq 0.1\%$ butadiene.

Dahl et al. 1988 – It is not clear if the rats were exposed to Isobutane, Isopentane and Butane at the same time, or if different groups of rats were exposed to one compound. The results of this study are not clear. For example, if uptake and flow rate are stated, and the results for Isobutane are given at 2 concentrations, why are only 3 values stated? There should be 2 values for 100 ppm and 2 values for 10 ppm.

ECHA dossier on Isobutane, Acute – If the exposure period was only 4 hours, it does not make sense to state that “female body weight was reduced throughout the exposure period” (maybe it should be the observation period which is generally 14 days).

ECHA dossier on Isobutane, Acute – Although the original CIR report may not have specifically mentioned “effects on the central nervous system” it does discuss anesthetic effects, which are central nervous system effects. It is not correct to state: “Effects on the central nervous system were not mentioned in the previous report.”

ECHA dossier on 2-methylbutane, Short-term – If no effects were observed, there should have been a NOAEC. Did the ECHA dossier say that a NOAEC was not identified, or did they just not identify a NOAEC?

ECHA dossier on Isobutane, Subchronic – In the reproduction paragraph it says: “five sections taken at least 100 ppm apart from the inner third of each ovary” – the units “ppm” do not seem to be correct, something like μm would make more sense.

McKee et al. 2014, DART – It is not clear if the rats were exposed to Isobutane, Butane, and Propane at the same time, or if there were separate groups exposed to only one compound.

t-Butyl Alcohol

In addition to dose, it would have been helpful to include the concentration in products used in the RIFM safety assessment (95th percentile in fine fragrances 0.019%).

No Comments

Laneth-9 Acetate and Laneth-10 Acetate

Acacia Senegal Gum and Acacia Senegal Gum Extract

Zinc Phenolsulfonate



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc., Senior Scientific Analyst/Writer, CIR
Date: August 31, 2023
Subject: Safety Assessment of Benzaldehyde as Used in Cosmetics

Enclosed is a comment from Council on the re-review summary of the Safety Assessment of Benzaldehyde as Used in Cosmetics. The Council has suggested that the Panel include a stronger statement about Benzaldehyde being used within International Fragrance Research Association (IFRA) standards.



Memorandum

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

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

DATE: August 29, 2023

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

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

Benzaldehyde

It would be helpful if the re-review summary included a stronger recommendation about the IFRA standard such as: "No matter the function of Benzaldehyde in cosmetic products, the Expert Panel for Cosmetic Ingredient Safety recommends that the IFRA standard based on sensitization potential of Benzaldehyde be followed."

No Comments

Polyquaternium-11



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, MS, Senior Scientific Analyst/Writer, CIR
Jinqiu Zhu, PhD, DABT, ERT, DCST, CIR Toxicologist
Date: August 31, 2023
Subject: Wave 2 - WVE's comments on the strategy memo on Toluene literature selection

The comments received from Women's Voices for the Earth (WVE) on August 30, 2023, regarding the strategy memo on Toluene literature selection, are forwarded in this Wave 2 submission to the Panel. CIR plans to respond to these comments in full at a future meeting, but the following is noted for the Panel.

In their comments, WVE stated that the CIR review on Toluene should incorporate occupational exposure studies, specifically mentioning "...several occupational studies of toluene exposure in salon workers...which must be included." Please note that one of the studies listed in the bibliography (Choi et al 2023¹) specifically examined extensive exposure to 13 volatile organic compounds (VOCs), including toluene, as well as 11 carbonyl compounds in beauty salon environments.

In addition, WVE disagreed with the risk assessment methodology employed by the Danish Environmental Protection Agency (EPA) for evaluating the safety of chemical substances in nail products. WVE argued that, given the high usage rates of nail polish among young girls in California, the assumption that only 9% of the applied product would affect the surrounding skin underestimates the potential dermal exposure in children. WVE further pointed out "*a recent risk assessment² on exposure to toluene from hand sanitizers simply used 100% dermal exposure as a conservative estimate due to uncertainties in absorption.*" It is important to clarify, however, that WVE conflated 100% dermal permeation rate with 100% dermal exposure. Further scrutiny of the cited risk assessment reveals that the authors applied a conservative 100% figure for the dermal permeation rate of benzene when co-exposed with alcohols during hand sanitizer use; this does not necessarily mean that 100% of applied nail products would be absorbed into the human body. When calculating dermal exposure doses from hand sanitizer use, it may be reasonable to assume 100% of the product contacts human skin; however, this is not a valid assumption for incidental dermal exposure related to nail products.

WVE also believed that the Danish EPA's methods "*underestimate the potential for toluene inhalation from the use of cosmetics.*" To support their argument, WVE provided the following data "*the average toluene levels measured in air during nail coating application ranged from 3,200 to 9,200 µg/m³ (850 ppb to 2,400 ppb), while the post-application concentrations ranged from 200 to 1,700 µg/m³ (50 to 450 ppb).*"³ According to the Danish EPA's evaluation, roughly 25% of the nail product's total formaldehyde content is expected to evaporate while drying. Of that amount, it is assumed that half (12.5%) would be inhaled. As a result, no more than 21.5% of the total formaldehyde content (9% through skin absorption and 12.5% via inhalation) would be available to contribute to the overall systemic exposure. The same amount was assumed for Toluene (as Toluene is less volatile than formaldehyde) in the risk assessment included in the Toluene literature selection Strategy Memo.

Although CIR is planning to formally respond to the WVE comments with the future Draft Amended Report on Toluene, the Panel is requested to take the submitted comments into consideration during its discussion of the Strategy Memo.

References:

1. Choi YH, Kim HJ, Sohn JR, Seo JH. Occupational exposure to VOCs and carbonyl compounds in beauty salons and health risks associated with it in South Korea. *Ecotoxicol Environ Saf* 2023;256:114873.
2. Pal VK, Lee S, Naidu M, Lee C, Kannan K. Occurrence of and dermal exposure to benzene, toluene and styrene found in hand sanitizers from the United States. *Environ Int* 2022;167:107449.
3. Curry KK, Brookman DJ, Whitmyre GK, et al. Personal exposures to toluene during use of nail lacquers in residences: Description of the results of a preliminary study. *J Expos Anal Environ Epidemiol* 1994; 4(4):443-45.

August 30, 2023

To the CIR:

I am writing to submit comments on the Strategy Memo on Toluene Literature Selection.

While I certainly understand the significant numbers of studies on toluene that are available to the CIR staff to review, and the desire to prioritize important papers, I encourage you not to dismiss any more research than necessary. Toluene is a considerable chemical of concern, and its prevalent use in cosmetics is highly controversial.

Unlike many other cosmetic ingredients, toluene has been listed as a chemical of concern by multiple governmental authorities:

- Identified both as a priority pollutant and a toxic pollutant under the federal Clean Water Act
- Identified as a neurotoxicant in the Agency for Toxic Substances and Disease Registry's Toxic Substances Portal
- Identified as a chemical for which a reference dose or reference concentration has been developed based on neurotoxicity in U.S. EPA's Integrated Risk Information System (IRIS)
- Identified on the U.S. Centers for Disease Control and Prevention's Fourth National Report on Human Exposure to Environmental Chemicals
- Identified as a toxic air contaminant by CARB (California Air Resources Board)
- Identified with noncancer endpoints and listed with an inhalation Reference Exposure Level (REL) by the California Office of Environmental Health Hazard Assessment (OEHHA) under Health and Safety Code section 44360(b)(2)
- Listed as a developmental toxicant under CA Proposition 65 (Safe Drinking Water and Toxic Enforcement Act of 1986)
- Identified as a chemical for which a primary Maximum Contaminant Level (MCL) has been established and adopted under section 64431 or section 64444 of Chapter 15 of title 22 of the California Code of Regulations

1) Occupational exposure studies are relevant to the CIR's review

Particularly, I am concerned about the suggestion in the strategy memo to exclude studies of occupational exposure from the review, claiming "the exposure scenarios involved are irrelevant to cosmetic use". As you know, generally, exposure studies on casual exposure to toxic chemicals (for example from consumer use of cosmetics) are few and far between. Occupational studies are therefore very important for providing context from which extrapolations can be made. Certainly, there are several occupational studies of toluene exposure in salon workers, that are highly relevant to your review, which must be included.

To help narrow down relevant studies, it may be helpful for the CIR staff to review recent documents produced by the California Department of Toxic Substances Control (DTSC) specifically on Nail Products containing Toluene:

<https://dtsc.ca.gov/scp/nail-products-containing-toluene/>

Just this year, the DTSC established an Alternatives Analysis Threshold of 100ppm toluene for all nail products sold in California. In their scientific review of toluene they stated:

*“...we have determined that **exposure to toluene through normal use of nail products may contribute to or cause significant or widespread adverse impacts to Californians, including sensitive subpopulations such as nail salon workers, pregnant women and their fetuses, infants, children, and adolescents.**”*

Their final report, with an extensive bibliography on health effects of toluene, including numerous relevant occupational studies can be found here: https://dtsc.ca.gov/wp-content/uploads/sites/31/2023/06/Profile_Toluene-in-Nail-Products_FINAL.pdf

2) Danish EPA exposure calculation is likely to significantly underestimate exposure

I am also concerned about the suggestion of using the exposure calculation method from the Danish EPA safety assessment which appears to me to likely underestimate potential exposure. For one – the calculation suggests just one application of nail product containing toluene per day. Studies have shown toluene to be present in nail polish remover, base coats, top coats, nail polish thinner, gels and more. A person could easily use multiple products in one sitting (removing old nail polish, applying a base coat and then a top coat for example) potentially tripling the exposure that would have been calculated by this method. Also, the Danish calculation does not take into account potential exposures to children from nail products. A study in California found that nail polish use was common among children: 45 percent of girls age 5 and under and 79 percent of girls over 5 used nail polish.ⁱ Given that, and the knowledge of how careful a 5 year old might be with nail polish, the estimate of “9% of the applied nail product will cover the skin surrounding the nail” is likely a significant underestimate. A more conservative approach would be much more health protective. For example, a recent risk assessment on exposure to toluene from hand sanitizers simply used 100% dermal exposure as a conservative estimate due to uncertainties in absorption.ⁱⁱ The Danish method also appears to underestimate the potential for toluene inhalation from the use of cosmetics. As just one illustration, a study quoted in the DTSC analysis found that a single application of nail polish in a home setting significantly increased the levels of toluene in air samples in some cases by nearly 50-fold.

“Curry et al. (1994) described a personal monitoring study of inhalation exposure to toluene during normal in-home consumer use of nail coating products at five different residences in California. Prior to the nail coating application, toluene was not detected in any of the air samples above the detection limits of 200 µg/m³ (50 ppb) in air. However, the average toluene levels measured in air during nail coating application ranged from 3,200 to 9,200 µg/m³ (850 ppb to 2,400 ppb), while the post-application concentrations ranged from 200 to 1,700 µg/m³ (50 to 450 ppb).”

Citation: Curry KK, Brookman DJ, Whitmyre GK, et al. (1994) Personal exposures to toluene during use of nail lacquers in residences: Description of the results of a preliminary study. *J Expos Anal Environ Epidemiol* 4(4):443-45

Thank you for your consideration of these comments.



Alexandra Scranton
Director of Science and Research
Women’s Voices for the Earth

ⁱ Wu XM, Bennett DH, Ritz B, Cassady DL, Lee K, Hertz-Picciotto I (2010) Usage pattern of personal care products in California households. *Food Chem Toxicol* 48(11):3109-3119 doi:10.1016/j.fct.2010.08.004

ⁱⁱ Pal VK, Lee S, Naidu M, Lee C, Kannan K. Occurrence of and dermal exposure to benzene, toluene and styrene found in hand sanitizers from the United States. *Environ Int.* 2022 Sep;167:107449.



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Regina Tucker, M.S., Scientific Writer/Analyst, CIR
Date: August 31, 2023
Subject: Safety Assessment of *Zanthoxylum piperitum*-Derived Ingredients as Used in Cosmetics – Wave 2

Enclosed are the Council's comments on the Draft Final Report of the Safety Assessment of *Zanthoxylum piperitum*-Derived Ingredients, which are attached herein for the Panel's review (*PCPCcomments_ZanthoxylumPiperitum_Wave2_092023*). The Panel should review the language in the Discussion section on the absorption of *Zanthoxylum piperitum*-Derived ingredients and discuss if any edits or clarification should be made.



Memorandum

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

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

DATE: August 29, 2023

SUBJECT: Draft Final Report: Safety Assessment of *Zanthoxylum piperitum*-Derived Ingredients as Used in Cosmetics (draft prepared for the September 2023 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft final report, Safety Assessment of *Zanthoxylum piperitum*-Derived Ingredients as Used in Cosmetics.

Key Issue

Discussion – Does the Expert Panel for Cosmetic Ingredient Safety want to say that “these ingredients are not expected to absorb through the skin”. In contrast, the NICNAS assessment stated that “given the low molecular weight of the components....there is potential for *Zanthoxylum piperitum* extract to cross biological membranes.”

Additional Considerations

ADME – Only the results for the compounds from *Zanthoxylum piperitum* need to be included in the CIR report (the shogaol compounds are from ginger and the ginsenoside compounds are from ginseng).