# Communications Supplement

Airbrush Boilerplate

Amino Cresols RR

Amyl Acetate RR

Ginger

Glucosamine

GRAS Whitepaper

Prostaglandins Strategy Memo

Radish Root

Sage

EXPERT PANEL MEETING
June 16-17, 2022

WVE
WOMEN'S VOICES FOR THE EARTH

June 10, 2022

Re: Airbrush Boilerplate – Wave 2

To the CIR:

Upon review of the new airbrush boilerplate language, I have a few comments and a few questions about how the CIR plans to handle determinations of the safety of ingredients used in airbrush cosmetics in the future.

Currently, the new boilerplate language states:

> *"Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Therefore, airbrush application of cosmetic products is not assessed by the Panel."*

This represents the current state of knowledge on airbrush cosmetics – but, obviously, this could change if data on consumer habits and practices and/or particle size data does become available.

The boilerplate language also states:

> "*The Panel's respiratory exposure resource document (https://www.cir- safety.org/cir-findings) notes that airbrush technology presents a potential safety concern…"*

This leads me to a number of questions about the intentions of the CIR Expert Panel and its responsibility to manufacturers and cosmetic users alike for assuring the safety of cosmetic ingredients.

**If the Expert Panel is aware that a cosmetic ingredient when used in a certain type of cosmetic product presents a potential safety concern – which could in fact cause harm to users – what efforts will the Panel make to obtain the necessary information that could prevent the harm from occurring?**

For now, without further information available on airbrush cosmetics, the CIR can offer a public warning by stating in their conclusions:

> *"Thus, the data do not support the safety of the ingredients named in this report if applied via airbrush delivery systems."*

While this is very important language to include in a safety assessment, this language, apparently, will only be included in a CIR assessment when someone like me has notified the CIR that the ingredient appears to be present in airbrush cosmetics, because the official systems available to the CIR (i.e. the VCRP/Council survey) do not currently allow for the identification of ingredients in airbrush cosmetics.

PO Box 8743, Missoula, MT 59807 406.543.3747 www.womensvoices.org womensvoices@womensvoices.org

Again – this is only the current state of knowledge – if demanded, both the VCRP and or Council surveys could be changed to allow for the collection of the needed data that is crucial to prevent harm from exposure to cosmetic ingredients in airbrush cosmetics.

Similarly, if demanded, data on consumer practices and uses, as well as particle size data on cosmetic airbrush delivery systems could be generated. The CIR Expert Panel does have considerable leverage over the cosmetics industry, that as of yet, has only rarely been used.

**The question is – when there are substantial safety questions at hand, how much effort does the CIR Expert Panel feel they are responsible for making to obtain the information they need to make a full determination of safety?**

**Is the Expert Panel comfortable accepting the current lack of available information and allowing the potential harm from airbrush cosmetics to occur indefinitely?**

**Is the CIR Expert Panel washing its hands of the airbrush cosmetics problem by simply stating that "airbrush application of cosmetic products is not assessed by the panel"?**

**Or…**

**Will the CIR Expert Panel commit to continuing to pursue getting the information they need about airbrush cosmetics because the safety of users is on the line?**

(This could including making changes to how VCRP data is collected, asking for a Council survey on airbrush cosmetics, encouraging action by the CIR SSC to get needed data generated, and/or repeatedly demanding that the PCPC require pertinent information be submitted by their members about their airbrush cosmetic products and delivery systems.)

**In the meantime, will the CIR Expert Panel be more transparent and public about their concerns of the safety of cosmetic ingredient applied by airbrush delivery systems?**

**What would the CIR Expert Panel want a current daily user of airbrush cosmetics to know about their respiratory exposures, given the current lack of complete information?**

**What does the CIR Expert Panel want manufacturers to know about how they should approach the use of cosmetic ingredients in airbrush cosmetics?**

Thank you for your consideration of these comments.

Sincerely,

Alexandra Scranton
Director of Science and Research

*Commitment & Credibility since 1976*

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Monice M. Fiume
Senior Director, CIR
Jinqiu Zhu, PhD, DABT, ERT, DCST, CIR Toxicologist
Date: June 13, 2022
Subject: Response to WVE's comments on airbrush boilerplate

Enclosed are comments received from Women's Voices for the Earth (WVE) dated June 10, 2022, on the new airbrush boilerplate language submitted for the Panel's review in Wave 2.

Broadly, WVE asked whether the Panel will commit to continuing to pursue getting necessary information to evaluate ingredient safety as used in airbrush cosmetics; and what efforts the Panel will take to get the necessary data to prevent harm that could potentially result from application of cosmetics delivered via airbrush systems. WVE also wondered what the consumer should know about their daily potential inhalation exposure to airbrush products, and how the manufacturers should approach the use of substances in airbrush cosmetics. In addition, WVE queried the transparency of the review process and public accessibility of the Panel's concerns and conclusion.

First and foremost, it should be emphasized the Panel attaches great importance to the inhalation risks that may result from usage of cosmetic products through airbrush delivery systems. When it was recognized that some cosmetic substances can be used in cosmetic products that can be applied via airbrush delivery systems, and thereby associated with prolonged inhalation exposure to micro- to nano-sized particles, the Panel put significant efforts into addressing safety issues that are related to ingredient usage in the product categories of propellant driven sprays and airbrush delivery systems. The Panel discussed relevant concerns robustly at the December 2020, September 2021, December 2021, as well as March 2022, meetings. During this process, the Panel requested, and subsequently carefully reviewed and issued, the updated CIR Inhalation Resource Document, which incorporated new data on characterization of deposited dose of inhalable aerosols released from relevant airbrush delivery systems. Importantly, warnings are presented in the CIR Respiratory Exposure Resource Document regarding the respiratory exposure to aerosols released during usage of airbrush products:

> Therefore, the use of **airbrush** devices would result in inhalation exposure to single nanosized particles and multi-sized agglomerates, including complex nanoparticle-containing composites, which may **present unknown health risks**. (see pdf page 6 of CIR Respiratory Exposure Resource Document at https://www.cir-safety.org/sites/default/files/report_InhalationDocument_122021.pdf)

> The Panel recognized nano-enabled consumer products have a complex mixture that contains many elements, and **airbrush** applications might result in inhalation exposure to nanosized metal oxides, such as $TiO_2$ and $Fe_2O_3$, which **poses public health risks**. (see pdf page 7 of CIR Respiratory Exposure Resource Document at https://www.cir-safety.org/sites/default/files/report_InhalationDocument_122021.pdf)

Accordingly, the Panel clearly clarifies a standpoint in updated airbrush boilerplate:

> The Panel's respiratory exposure resource document (https://www.cirsafety.org/cir-findings) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. Thus, the data **do not support** the safety the ingredients named in this report if applied via airbrush delivery systems.

Please note the following statements have already been presented in CIR Respiratory Exposure Resource Document, which clearly declare the Panel's motion, commitment, as well as continuing data requirement for the purpose of better conducting a risk assessment for airbrush relevant cosmetic products:

> As more nanotechnology based consumer products are being formulated and released into the market, in order to **determine safety for the discrete ingredient** used in aerosolized consumer products that are **specially delivered through airbrush systems** or other nano-enabled aerosol canisters, **data requirements for inhalation risk evaluation would include** characteristics of airborne particles, such as the final particle size (and size distribution) of a spray product, the maximum use concentration of ingredient, and information on methods of use and spray characteristics (e.g., exposure duration and frequency, and technical details of spray equipment), as well as inhalation toxicity testing data, if necessary.
> (see pdf page 7 of CIR Respiratory Exposure Resource Document at https://www.cir-safety.org/sites/default/files/report_InhalationDocument_122021.pdf)

> The Panel will **continue to review all of the relevant** inhalation toxicity, use, and other data to determine the safety of cosmetic ingredients. The Panel will evaluate the importance of the inhalation route for assessing the safety of an ingredient or group of ingredients, and **evaluate data that may be available** to estimate potential respiratory doses from aerosolized products. **Factors to consider include** whether or how much of the spray products enter the breathing zone, the likely droplet/particle size distributions in the breathing zone, and the exposure durations that can be expected during product use.
> (see pdf page 11 of CIR Respiratory Exposure Resource Document at https://www.cir safety.org/sites/default/files/report_InhalationDocument_122021.pdf)

> If substances are meant to be included in sprays or aerosols, evaluation of consumer exposure via inhalation is paramount in the overall safety assessment. If inhalation toxicity data **are absent** or provide an insufficient basis to support the safety of an ingredient used in products that may be aerosolized, the Panel will **evaluate the sufficiency of other data** that may be available on a case by-case basis.
> (see pdf page 12 of CIR Respiratory Exposure Resource Document at https://www.cir-safety.org/sites/default/files/report_InhalationDocument_122021.pdf)

The CIR Science and Support Committee (CIR SSC) of the Council also noted in their comments (emphasis added) that were included in the Wave 2 Data Supplement (https://www.cir-safety.org/sites/default/files/Supplement_Wave2_062022.pdf): "The boilerplate language should make it clear that **habits** and **practices data** and **particle size information** on airbrush products are needed to estimate exposure." The following discussion included in CIR Respiratory Exposure Resource Document represents such consideration:

> As airbrush technologies have become increasingly popular for consumer product use, however, little guidance has been developed by regulatory authorities across the world to address safety concerns relating to potential exposure of the consumer via the inhalation route. A generic airbrush set typically consists of a trigger-controlled spray painting gun, an air compressor to create airflow, and a hose connector. The **airbrush pressure can be adjusted** to apply various types of makeup products, such as lighter, heavier, or more detailed styles. As a result, **spray parameters resulting from airbrush use** are triggered by individual habits and are highly sensitive to the exposure situation (e.g., particle/droplet size distribution at spraying, ventilation rate, room volume, frequency and duration, etc.). To **build realistic exposure scenarios**, it is therefore important to understand how each type of nano-enabled spray is realistically applied.
> (see pdf page 7 of CIR Respiratory Exposure Resource Document at https://www.cir-safety.org/sites/default/files/report_InhalationDocument_122021.pdf)

We note that this lack of exposure information precludes the ability to take a risk-based approach to safety assessment.

It should be noted that to protect consumers from potential risks arising from the application of cosmetics via airbrush delivery systems, a joint effort between multiple government agencies, such as US Consumer Product Safety Commission (CPSC) and the US Food and Drug Administration (FDA), as well as regulatory support, is required. In this regard, significant efforts have been made by CIR, as well as by the Panel, to clarify current federal regulations relating to the categorization and safety management of consumer products applied with airbrush delivery systems, and thus to clarify the purview of each agency or organization for their designated roles in face of such unprecedented challenges. For example, responses have been obtained from the US FDA Center for Devices and Radiological Health as well as the Office of Cosmetics and Colors (see page 16 – 19 at https://www.cir-safety.org/sites/default/files/Wave2_122021.pdf), and US Consumer Product Safety Commission (CPSC, see page 9 – 11 at https://www.cir-safety.org/sites/default/files/DataSupplement_wave2_032022.pdf). Based on these communications and responses, the following statements are included in the updated airbrush boilerplate:

> Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Therefore, airbrush application of cosmetic products is not assessed by the Panel.

Also, it has been clarified in the CIR Respiratory Exposure Resource Document that "the purview of the Panel is exclusive to assessing the safety of ingredients as used in cosmetics. Assessing the safety of devices, such as airbrush delivery systems, is obviously outside of that purview" (see pdf page 11 of CIR Respiratory Exposure Resource Document at https://www.cir-safety.org/sites/default/files/report_InhalationDocument_122021.pdf).

Furthermore, some issues raised by WVE's current comments have already been discussed and addressed in the CIR Respiratory Exposure Resource Document, as well as in CIR's responses to their previous comments. For instance, titanium dioxide ($TiO_2$) was listed as an ingredient in most cosmetic formulations submitted by WVE in their memo dated February 21, 2022 (pdf page 4 – 8 at https://www.cir-safety.org/sites/default/files/DataSupplement_wave2_032022.pdf), and recent research findings suggest it can be emitted into the consumer breathing zone in nano-form during airbrush applications. As the Panel discussed in Respiratory Exposure Resource Document,

> The Panel recognized nano-enabled consumer products have a complex mixture that contains many elements, and airbrush applications might result in inhalation exposure to nanosized metal oxides, such as $TiO_2$ and $Fe_2O_3$, which poses public health risks. For instance, $TiO_2$ is **classified** as a "Carcinogen Category 2 (inhalation)" by the European Commission, and in the EU, several nanomaterials (e.g., nano form of $TiO_2$, ZnO and carbon black) are **not allowed** to be used in applications that may lead to exposure of the end-user's lungs by inhalation. Based on this evidence, to be determined safe, application of cosmetics via airbrush technologies warrants further, extensive evaluation. Such evaluation of device use is outside the purview of the Panel review process.
>
> (see pdf page 7 of CIR Respiratory Exposure Resource Document at https://www.cir-safety.org/sites/default/files/report_InhalationDocument_122021.pdf)

However, $TiO_2$ is NOT prohibited for use in airbrush aerosols or other nano-sprays by the US FDA, and based on current available evidence, it has often been found in airbrush makeup products. Therefore, under current regulatory conditions, even if additional data on consumer habits and practices as well as particle size are submitted by Industry, consumers may yet face health risks when airbrush formulations contain such metal nanoparticle that could lead to respiratory exposure, during product use.

Similar discussion can also be identified in previous CIR response to WVE's comments, as illustrated below:

> As indicated by US CPSC in their message, "[I]f the hazard is associated with inhaling/ingesting the cosmetic that was airbrushed, addressing that hazard would likely fall under FDA's jurisdiction. However, if the hazard involved the airbrush device itself, addressing the hazard would likely fall within CPSC's jurisdiction." The following characteristics of airbrush devices should be considered on the variations between jurisdictions over different federal agencies:
>
> 1. based on currently available data, airbrush applications are associated with prolonged duration exposure to airborne nanosized particles;
> 2. nano-enabled consumer airbrush products have a complex mixture that contains many elements, and airbrush applications might result in inhalation exposure to nanosized metal oxides, such as $TiO_2$, which is classified as a "Carcinogen Category 2 (inhalation)" by the European Commission, and not allowed to be used in applications that may lead to exposure of the end-user's lungs by inhalation.
>
> It would seem that the US CPSC has confirmed that airbrush devices alone (i.e., not including what chemicals/ingredients are applied with the devices) are within its purview. However, cosmetic ingredients (including as used in airbrush devices), are yet within the jurisdiction of the US FDA, and thus the purview of this Panel. As stated in the updated Inhalation Resource Document, the "available data, however, are insufficient to determine median particle sizes (and distributions) resulting from airbrush device use." (This is merely one example, as the use of these devices is also insufficient for other relevant inhalation exposure/toxicity parameters and endpoints.) Thus, unless manufacturers provide relevant inhalation safety data, specific to the cosmetic ingredients used and the specific airbrush device used, all future assessments comprising airbrush use will result in insufficient data conclusions.

(see pdf page 2 – 3 at https://www.cir-safety.org/sites/default/files/DataSupplement_wave2_032022.pdf )

All these discussions aim at clarifying that protecting the consumer from potential risks arising from the application of cosmetic via airbrush delivery systems requires combined efforts and regulatory implementation from various government agencies and departments, as pointed out above. Ultimately, the use of any cosmetic ingredient in airbrush delivery systems is not supported by the available data.

WVE has submitted multiple comments regarding the health concerns associated with inhalation exposure when cosmetic ingredients are used with airbrush delivery systems, as well as on CIR Respiratory Exposure Resource Document. Each time, CIR staff have made significant efforts in responding to those concerns, and every comment has been taken seriously by the Panel and further discussed and addressed at the Panel meetings. It needs to be pointed out the whole review and responding process are transparent and open for public access. For example, the following links lead to comments submitted by the WVE, and the corresponding annotations and responses drafted by CIR staff:

pdf page 3 – 13 at https://www.cir-safety.org/sites/default/files/Inhalation.pdf (Materials of 159th Expert Panel Meeting, December 2021)
pdf page 32 – 43 at https://www.cir-safety.org/sites/default/files/Wave2_122021.pdf (Materials of 159th Expert Panel Meeting, December 2021)
pdf page 2 – 8 at https://www.cir-safety.org/sites/default/files/DataSupplement_wave2_032022.pdf (Materials of 160th Expert Panel Meeting, March 2022)

Concerns and issues raised by WVE in those comments have been addressed and answered conscientiously and carefully from a scientific perspective.

Finally, it should be recognized that manufactures who market cosmetics have a legal responsibility to ensure the safety of their products, and thus it is the continuing responsibility of the manufactures to ensure that marketed products are safe and compliant with all applicable legal and regulatory requirements.

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:** June 10, 2022

**SUBJECT:** Re-review: Amino Cresols (June 2022 meeting draft)

The Personal Care Products Council respectfully submits the following comments on the amino cresol hair dye ingredients re-review.

Please review the EU limits for these hair dye ingredients. The memo states 4-Amino-m-Cresol is in Annex II. 4-Amino-m-Cresol is in Annex III with a limit of 1.5% in oxidative hair dyes. This is correctly stated in the table. Although Cosing does not included a limit for 5-Amino-6-Chloro-o-Cresol in oxidative hair dyes, the original regulation at Commission Regulation (EU) No 1197/2013 of 25 November 2013 amending Annex III to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic productsText with EEA relevance (europa.eu) includes a limit of 1% for oxidative hair dyes in the "Other" column. This is incorrectly presented in both the memo and the table. In the Disclaimer, the Cosing user manual states: "The Institutions do not assume any liability for the content of this database. Only information provided by Cosmetics Regulation (EC) No 1223/2009, and its amendments, have a legal value." Therefore, the amendment rather than Cosing should be cited.

Table, 6-Amino-m-Cresol – Please state the organs that were examined microscopically, or state the guideline followed if this was a guideline study.

Table, 6-Amino-m-Cresol, Genotoxicity – in vivo – Units of mg/kg bw should be called doses rather than concentrations.

Table, 4-Amino-m-Cresol, Margin of Safety – Please state the use for which the margin of safety was calculated.

Table, 4-Chloro-2-Aminophenol, Carcinogenicity – Please indicate if the mouse study was a dietary or drinking water study.

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:** June 10, 2022

**SUBJECT:** Re-review: Amyl and Isoamyl Acetates (June 2022 meeting draft)

The Personal Care Products Council respectfully submits the following comments on the re-review of Amyl and Isoamyl Acetates.

It would be helpful to mention the functions as listed in the Dictionary as part of the re-review document.

In the column that describes the studies, please identify the guideline, if it was a guideline study. If the study did not follow a guideline, the endpoints examined in the study should be stated. What "toxic effects" were reported in the original report in rats and cats exposed by inhalation to Amyl Acetate?

In the second subchronic inhalation study of Amyl Acetate, how many hours/day were the rats exposed?

Please provide some indication of uses/concentrations considered safe in the RIFM assessments. Are the use concentrations reported in the PCPC survey within the use concentrations reported by RIFM?

CIR does not assess environmental safety. Therefore, it is not clear how the RIFM conclusion of "not persistent, bioaccumulative or toxic per IFRA Environmental Standards", "supports CIR's previous conclusion as safe as used for this ingredient."

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:** June 10, 2022

**SUBJECT:** Draft Tentative Report: Safety Assessment of *Zingiber officinale* (Ginger) – Derived Ingredients as Used in Cosmetics as Used in Cosmetics (June 2022 meeting draft)

The Personal Care Products Council respectfully submits the following comments on the draft tentative report, Safety Assessment of *Zingiber officinale* (Ginger)–Derived Ingredients as Used in Cosmetics.

Key Issue
This report does not make it clear that the chemical class for Zingiber Officinale (Ginger) Root Oil is essential oils and waters. As both the fixed oil and essential oil are mentioned in the CIR report, somewhere in the report, it should state that the INCI name represents the essential oil not the fixed oil.

Additional Considerations
Introduction – Root and rhizome of ginger are being used interchangeably in INCI names. The last sentence of the Introduction should be deleted.

Method of Manufacture – This section implies that it is unknown if the methods apply to cosmetic ingredient manufacture. Please be more specific and state that it is unknown if the methods found in published papers apply to cosmetic ingredients. The methods from suppliers do apply to cosmetic ingredients.

Method of Manufacture, Zingiber Officinale (Ginger) Root – The information in this subsection concerns composition and should be moved to the Composition and Impurities section.

Non-cosmetic Use – Rather than stating that the essential oil is "used at a concentration of 100%", it should state that it is "sold at concentration of 100%". It is diluted before use.

Developmental and Reproductive – The descriptions of the dosing periods for the pre-implantation versus post-implantation studies appear to be transposed. To assess effects on pre-implantation, the mice need to be dosed before mating. The exposure period for "post-implantation effects" is currently stated as "mice (10/group) treated 20 d before, and throughout gestation" while "pre-implantation effects" is incorrectly with "20 d throughout gestation". If the mice are treated after implantation, it is not possible to assess "pre-implantation effects". If mice are treated before and during gestation, it may not be possible to distinguish between pre- and post-implantation effects.

Dermal Irritation and Sensitization – Please state the number of subjects used in the study of the product containing 0.2% Zingiber Officinale (Ginger) Root Extract.

Case Reports – In the description of reference 69, please revise the following to make it clear that each spice was tested in a different chamber. "Eleven spices (including powdered ginger) were put on a filter paper in a test chamber, moistened with a drop of water, and placed on the back, under occlusion."

Summary – Please indicate when in relationship to mating the mice were treated with 2000 mg/kg rhizome extract and decreases in implantation sites were observed.

Table 8 – Reference 66 indicated that the test article (a moisturizer) was used. The test material section states: "The test article was volatilized at least 30 minutes, but less than 90 minutes on the patch prior to application to the skin". This information should be included in Table 8.

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:** June 10, 2022

**SUBJECT:** Draft Final Report: Safety Assessment of Glucosamine Ingredients as Used in Cosmetics (June 2022 meeting draft)

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

Abbreviations – The definition for $T_{max}$ needs to be corrected from "time to reach serum concentration" to "time to reach maximum concentration"

Subchronic, Animal, Oral – In the description of the 13-week study of Acetyl Glucosamine in rats (reference 28), please state which organs were examined microscopically, or if this is a guideline study, please state the guideline that was followed.

Reduction of IgE-Mediated Hypersensitivity, Acetyl Glucosamine and Glucosamine HCl – This section states: "the amount of histamine in the plasma of the right ear was measured" and "reduced the concentration of histamine in both the ear and plasma of DNFB-treated mice". The second statement needs to be revised to make it clear that only one histamine measurement was completed.

Summary – Please revise: "reduction of facial hyperpigmentation after topical treatment on Acetyl Glucosamine"("on" should be "with"). Please correct: "Similarly, no sensitization was in maximization assays" (please add the word "observed").

WOMEN'S VOICES FOR THE EARTH

June 9, 2022

Re: Draft Whitepaper on GRAS Determination and its role in the safety assessment of cosmetic ingredients

To the CIR:

The draft GRAS whitepaper provides an important perspective on the meaning and influence of a GRAS determination on understanding the safety of a cosmetic ingredient. It is clear from the whitepaper, that some GRAS determinations are considerably less robust that others, and often do not provide sufficient evidence of safety of an ingredient. There are numerous other available critiques of the GRAS system that the CIR panel should be aware of – which also raise considerable doubts as to the usefulness of GRAS determinations in establishing the safety of an ingredient. Information from these critiques would also be useful to add to the CIR's whitepaper.

Specifically, critiques of the GRAS program include:

U.S. Government Accountability Office: Food Safety: FDA Should Strengthen Its Oversight of Food Ingredients Determined to be Generally Recognized as Safe (GAS)

https://www.gao.gov/products/gao-10-246

> *"FDA is not systematically ensuring the continued safety of current GRAS substances. While, according to FDA regulations, the GRAS status of a substance must be reconsidered as new scientific information emerges, the agency has not systematically reconsidered GRAS substances since the 1980s."*

NRDC: Generally Recognized as Secret: Chemicals Added to Food in the United States

https://www.nrdc.org/sites/default/files/safety-loophole-for-chemicals-in-food-report.pdf

Broken GRAS: Undermining the safety of dietary supplements and food

https://blogs.edf.org/health/2021/09/27/broken-gras-undermining-the-safety-of-dietary-supplements-and-food/

GRAS: The Hidden Substances in Your Food

https://www.consumerreports.org/food-safety/gras-hidden-ingredients-in-your-food/

It is concerning then, that the CIR has a practice of dismissing the need for additional toxicity data, because an ingredient has a GRAS determination.[i] This practice affirms that the CIR has previously believed a GRAS determination assures safety (or lack of toxicity) which is an unjustified assumption in many cases. It is not at all clear that a GRAS determination ensures that FDA has already reviewed, considered and cleared the many types of toxicity that the CIR reviews for every ingredient.

PO Box 8743, Missoula, MT 59807 406.543.3747 www.womensvoices.org womensvoices@womensvoices.org

It is a disservice to both cosmetic manufacturers and to public health at large to intentionally limit the review of toxicity data, by making assumptions of safety based on what largely appears to be the flawed GRAS program of the FDA. Dismissing the need to review important toxicity data could lead to a faulty determination of safety by the CIR putting both manufacturers and cosmetic users at risk. The CIR can take the GRAS determination into account in their review if they wish– but it should not replace the need for review of toxicity data, that may or may not have been taken into account when the GRAS determination was made. It appears that actually accessing details on the data the FDA did review in making a GRAS determination is not easily done, and likely impossible for self-determined GRAS determinations made by the manufacturers. And in any case, many GRAS determinations are years if not decades old, meaning that new toxicity data generated since the determination was made could be available and pertinent to the CIR's review, and should not be dismissed.

I would recommend that the GRAS whitepaper include more specifics about how a GRAS determination can be considered by the CIR. Specifically, the white paper should clarify that a GRAS determination should never replace the need for additional toxicity testing that is missing from a draft report.

Thank you for your consideration of these comments.

Alexandra Scranton
Director of Science and Research

---

[i] Recent examples of the CIR dismissing the need of additional toxicity data of GRAS ingredients include:

1) CIR meeting September 2021 discussion of Glycolactones:
https://cir-safety.org/sites/default/files/Glycolactones_0.pdf (p. 11 of 43)

"DR. COHEN: All right, we'll ask for the information. Ron, do you agree we need irritation sense for max use?
DR. SHANK: For the Glucarolactone, yes.
DR. COHEN: Right, well, we don't have anything else on it.
DR. SHANK: It's a GRAS compound, so we don't need anything else.
DR. SLAGA: Right.
DR. COHEN: Okay…

DR. SHANK: Yeah, sorry. What I was trying to say and didn't was there are no other data needs besides sensitization, because of the GRAS status"

2) Safety assessment of Rosa damascena-Derived Ingredients as Used in Cosmetics – Final Report April 13, 2022

*"**The need for systemic toxicity data was mitigated,** as all of the ingredients described in this report are composed from plant parts that are used in foods or are considered GRAS for intended food use, according to the US FDA. Since systemic exposure from food is expected to be far greater than exposure via cosmetics, the Panel considered the toxicity data in this review sufficient."*
*"No relevant toxicokinetic studies on Rosa damascena-derived ingredients were found in the published literature, and unpublished data were not submitted."*
*"Developmental and reproductive toxicity studies were not found in the published literature, and unpublished data were not submitted."*
*"Carcinogenicity studies on the Rosa damascena-derived ingredients were not found in the published literature, and unpublished data were not submitted."*

Cosmetic Ingredient Review

*Commitment & Credibility since 1976*

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Jinqiu Zhu, PhD, DABT, ERT, DCST, CIR Toxicologist
Date: June 13, 2022
Subject: Response to WVE's comments on the draft whitepaper of GRAS status and the safety evaluation of cosmetic ingredients

Enclosed are comments received from Women's Voices for the Earth (WVE), dated June 9, 2022, on the draft whitepaper regarding GRAS determination and its role in the safety assessment of cosmetic ingredients.

At the March 2022 Panel meeting, the self-affirming mechanism of the US FDA GRAS notification program was clarified by a meeting attendee from the FDA. In the current comments, WVE further listed some links of critiques (one of which is from a blog) on the FDA GRAS notification program. The Panel noted such concerns and issues raised by various organizations and therefore requested a whitepaper be drafted to clarify the Panel's view on GRAS determination, as well as how a GRAS determination can be considered in the safety assessment of cosmetic ingredients. Thus, the draft whitepaper briefly summaries current regulations and rules on GRAS determination, and introduces how to apply GRAS status as a safety factor for cosmetic ingredient safety; clarifications were further provided on some of the key elements to evaluate the safety of cosmetic substances that are subject to self-affirmed GRAS conclusion (under three respective sections).

WVE recommended in the comments that "Specifically, the white paper should clarify that a GRAS determination should never replace the need for additional toxicity testing that is missing from a draft report." Please note, the following statements and discussions have already been presented in the draft whitepaper:

> Therefore, regardless of whether a safety conclusion has been reached for a GRAS notice, **the available data and information** with the notified substance (as well as self-certified GRAS substances without notifying the FDA) **warrant further evaluation** to consider the intended use as an ingredient in cosmetic products. Whether supporting materials included in a GRAS notice satisfy the criteria for GRAS status through scientific procedures is a case-by-case determination. Thus, **caution should be taken** when utilizing reference points associated with self-certified GRAS conclusions, specifically when conducting safety evaluation of ingredients under their intended use in cosmetic products.
>
> (see pdf page 7 at https://www.cir-safety.org/sites/default/files/Admin_GRAS_Whitepaper.pdf)

> The Panel notes **additional attention** should be given when exposure routes other than oral are investigated for **accessing the systemic toxic potential** of a cosmetic ingredient and determining the margin of safety.
>
> (see pdf page 3 at https://www.cir-safety.org/sites/default/files/Admin_GRAS_Whitepaper.pdf)

> The Panel notes that general recognition of safety, as well as evidence of GRAS status, must relate to the conditions of intended use. In addition, a substance must comply with specific usage limitations appearing in any GRAS determination. GRAS status may not be applicable if the conditions of use differ significantly from those providing the basis for eligibility. Thus, when using GRAS status as a factor in the safety assessment of cosmetic ingredients, it should be **considered with other relevant assessment factors** that contribute to the

determination of a safety margin on a case-by-case basis (such as route of exposure, use pattern, dose level, first-pass effect/metabolism, etc).

(see pdf page 4 at https://www.cir-safety.org/sites/default/files/Admin_GRAS_Whitepaper.pdf)

It has been recognized that the regulatory significance of a "no questions letter" warrants further clarification. The FDA's response must be considered in context **based on the data available to reviewers at a point in time**, because **scientific knowledge and information** about a particular ingredient can **evolve** and sometimes **change over time**.

(see pdf page 4 at https://www.cir-safety.org/sites/default/files/Admin_GRAS_Whitepaper.pdf)

Note, GRAS assessment is **dynamic** and **must be reevaluated** to account for new information on ingredients and new perspectives on safety evaluation. It has also been recognized that **toxicological data** relating to chemical substances that are used in products other than cosmetics, such as **food and medicines**, **can also be used** for supporting safety assessment of an ingredient intended to be used in a cosmetic product.

(see pdf page 6 at https://www.cir-safety.org/sites/default/files/Admin_GRAS_Whitepaper.pdf)

In addition, a conclusion of GRAS status claimed in a notice should be supported through the application of **scientific principles** for the safety assessment of food ingredients, as well as **based on data, information, or methods** that are generally available. Therefore, the Panel may consider **the application of a WoE approach**, for the oral-to-dermal extrapolation of available data and information for cosmetic uses.

(see pdf page 6 at https://www.cir-safety.org/sites/default/files/Admin_GRAS_Whitepaper.pdf)

**Data from oral animal toxicity studies** are commonly used to assess the safety of human dermal exposure scenarios. In some cases, a safety evaluation **based on data** included in self-affirmed GRAS notice may **require route-to-route extrapolation**, which may be associated with considerable uncertainties.

(see pdf page 7 at https://www.cir-safety.org/sites/default/files/Admin_GRAS_Whitepaper.pdf)

In the current comments, WVE claimed "the CIR has a practice of dismissing the need for additional toxicity data, because an ingredient has a GRAS determination." They used case assessments of Glycolactones and *Rosa damascena*-derived ingredients as negative examples to support such claim. Please note in both cases, the ingredients that WVE pointed out therein have been affirmed by the US FDA with GRAS status, and thus **NOT** subject to GRAS self-determination, i.e., Gluconolactone is a direct food substance affirmed as GRAS, with no other limitations other that current good manufacturing practices [21CFR1318]; according to 21CFR182.20, the essential oils, oleoresins (solvent-fee), and natural extractives/distillates of *Rosa damascena* rose absolute, rose otto, rose buds, rose flowers, and rose fruit are GRAS for their intended use in foods. That is, the Panel considered GRAS status through a *Code of Federal Regulations* (CFR) listing when reviewing those ingredients. Therefore, the following statements (as WVE quoted in their comments) included in the report are based on valid evidence and GRAS conclusion that have been verified by the FDA, "The need for systemic toxicity data was mitigated, as all of the ingredients described in this report are composed from plant parts that are used in foods or are considered GRAS for intended food use, according to the US FDA. Since systemic exposure from food is expected to be far greater than exposure via cosmetics, the Panel considered the toxicity data in this review sufficient." Please also note, the following discussions have already been presented in the draft white paper with regard to clarifying the Panel's view on substances with GRAS status affirmed by the FDA or self-determined by industry:

It should be clarified that substances included in GRAS lists recognized in *Code of Federal Regulations*, which currently appear in 21 CFR Parts 182, 184, and 186, have **different regulatory statuses** compared to the ones listed on the FDA inventory of GRAS notices, or others with independent GRAS conclusions without notifying the FDA.

(see pdf page 7 at https://www.cir-safety.org/sites/default/files/Admin_GRAS_Whitepaper.pdf)

> The inventory of GRAS notices, under the voluntary GRAS notification program, lists self-certified GRAS substances; the FDA's no question letters on GRAS notices **do not affirm** the GRAS status under Title 21 of the Code of Federal Regulations (21 CFR) 170.35.
>
> (see pdf page 3 at https://www.cir-safety.org/sites/default/files/Admin_GRAS_Whitepaper.pdf)

> The Panel is aware that the FDA's response to a GRAS notice **does not have the same level of authority** as a listing in the regulations. A "no questions letter" based on the FDA's evaluation of the entire GRAS notice, should be considered in the contexts of both time and the available data and information; while it should also be noted, at the time it is issued, the FDA verifies such a GRAS conclusion is in compliance with the statutory requirements for GRAS criteria, which is based on data and information that are generally accepted and accessible to the public (e.g., the conclusion is supported by the peer-reviewed scientific literature and publication in a textbook).
>
> (see pdf page 5 - 6 at https://www.cir-safety.org/sites/default/files/Admin_GRAS_Whitepaper.pdf)

Importantly, it deserves clarification that the Panel does not dismiss the need for all necessary toxicity data, and never conducted a safety evaluation merely based on GRAS determination. As stated in the draft whitepaper, "the Panel **performs a comprehensive safety evaluation** of the substance, and formally or informally, a sufficient margin of safety (MoS) based on the data available is to be determined on a **case-by-case basi**s. This scientifically constructed procedure **requires that all available relevant data should be used** in evaluating the safety of a substance under conditions of intended use as an ingredient in cosmetics. For ingredients under review, the maximum concentration of use and reported function(s) and route(s) of exposure from cosmetic products should be examined. **Wherever possible**, other uses of the substance (e.g., in food, consumer products, and industrial products), and the concentrations involved in such uses, **should be also considered**. Total aggregate exposure to a substance should be calculated based on exposure scenarios by using appropriate exposure models; as a first estimate for products intended for topical use, percutaneous absorption needs to be considered relevant to the amount of a substance that is applied to, or migrates to, a specified site (see pdf page 5 at https://www.cir-safety.org/sites/default/files/Admin_GRAS_Whitepaper.pdf)."

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:** June 10, 2022

**SUBJECT:** Draft White Paper: GRAS Status and the Safety Evaluation of Cosmetic Ingredients (June 2022 meeting draft)

The Personal Care Products Council respectfully submits the following comments on the draft white paper, GRAS Status and the Safety Evaluation of Cosmetic Ingredients.

It would be helpful to have examples of cosmetic ingredients that have been reviewed by CIR that are considered GRAS for a food use through both a CFR listing as well as an example of an ingredient that has a GRAS determination through the voluntary notification process.

In the section on Current Regulations and Rules on GRAS Determination it is not clear why the Federal Register notices are being cited rather than the current rules found in the Code of Federal Regulations e.g., 21CFR570.30. It is confusing that it states that the FR notice published in 1997 provides clarification when the more recent final rule was published in 2016.

GRAS Status as a Safety Factor Considered by the Expert Panel for Cosmetic Ingredient Safety – This section states that the Expert Panel for Cosmetic Ingredient Safety should consider "total aggregate exposure". The Expert Panel generally only considers exposure from the use of cosmetic products, not through other exposure scenarios. Please make this clear.

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:** June 10, 2022

**SUBJECT:** Strategy Memo: Prostaglandin Analogues – Eyelash Conditioning (June 2022 meeting draft)

The Personal Care Products Council respectfully submits the following comments on the strategy memo, Prostaglandin Analogues – Eyelash Conditioning.

The non-prostaglandin "eyelash conditioning agents" should not be included in this report. Ingredients should be grouped by structure, not cosmetic functions.

Tables 1 and 2: As "quasi drug" is not a function in the Dictionary, it should not be included in Tables 1 and 2 under reported functions. If the term "quasi drug" is used in a CIR report (or memo), it should be noted that it is a product category unique to Japan. It is not a category used in the United States. Does Japan consider these ingredients to be "quasi drugs"? If the objective of these tables is to indicate that Japan considers these ingredients to be "quasi drugs", this should be clearly stated.

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:** June 10, 2022

**SUBJECT:** Draft Final Report: Safety Assessment of Radish Root-Derived Ingredients as Used in Cosmetics (June 2022 meeting draft)

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

Abbreviations – In the list of abbreviations, OD is defined as Odds Ratio (OD usually means optical density). Odds ratio is usually abbreviated OR which is not in this report so it can be deleted from this list of abbreviations.

Method of Manufacture, Raphanus Sativus (Radish) Root Powder – As the radish root powder was not previously extracted, please delete the word "further".

Genotoxicity – Is reference 28 really a genotoxicity study? Although the study says "genotoxicity", the title indicates that they were looking at apoptosis, and the study indicates that they were looking at DNA fragmentation. If he has not done so already, it would be helpful to have Dr. Slaga look at this paper to see if the paper and the CIR report is using the correct terminology.

Dermal Irritation and Sensitization – This section should make it clear that a finished product containing 0.04% Leuconostoc/Radish Root Ferment Filtrate was tested undiluted. The description of this study in the Summary, is clearer than the description in the Dermal Irritation and Sensitization section.

Summary – Please revise the description of the phototoxicity study in the Summary. The following sentence does not make sense: "Significant reduction in cell viability (≥ 20 %) when compared to non-radiated controls, was seen at the 11% concentration, both with and without radiation; the test article was not considered a photoirritant." It should be noted that Leuconostoc/Radish Root Ferment Filtrate was not considered a photoirritant at concentrations less than 11%. It was possibly photoirritating at 11%.

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:** June 10, 2022

**SUBJECT:** Draft Final Report: Safety Assessment of *Salvia officinalis* (Sage)-Derived Ingredients as Used in Cosmetics (June 2022 meeting draft)

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

Method of Manufacture, Salvia Officinalis (Sage) Water – The definition for Salvia Officinalis (Sage) Water does not include a plant part. Therefore, "the leaves" needs to be deleted from this section.

Cosmetic Use – The airbrush language in the use section should be updated based on the comments provided by the CIR SSC (as was done for the other reports at the June meeting).

Developmental and Reproductive Toxicity; Summary – Please indicate that the mammary glands were examined (reference 34).

Developmental and Reproductive Toxicity – Please revise the following sentence: "Similarly, treatment with the *Salvia officinalis* leaf extract exhibited a significant dose-dependent increase in uterine weights." It was the treated rats that "exhibited" the changes, not the treatment.

Genotoxicity – Units of µg/ml should be called concentration rather than dose. If "91, 183, or 457 µg" are concentrations as stated, the volume units are missing. If the units are correct, this should be called a dose (is it µg/plate?).

Summary – Rather than stating "(unclear from source)", please state "(plant part not stated)". Please revise: "30-day oral dose" to "daily oral dose for 30 days".

Discussion – Is this what the Expert Panel intended to say: "*Salvia officinalis* leaves are the most constituent-rich ingredients, and therefore, would contain the highest levels of potential

sensitizers"? Since the data are insufficient for ingredients made from other plant parts, this sentence does not appear necessary, as the Expert Panel is not trying to read across from leaves to other plant parts.