Communications Supplement

2,4-Diaminophenoxyethanol

Copper Gluconate

Octoxynols

Phenylenediamine

Propylene Carbonate

EXPERT PANEL MEETING

March 13-14, 2025

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, MSES, Senior Scientific Analyst/Writer, CIR
Date: March 3, 2025
Subject: Wave 2 - Amended Safety Assessment of 2,4-Diaminophenoxyethanol HCl and 2,4-Diaminophenoxyethanol Sulfate as Used in Cosmetics

Please find attached the comments provided by the Personal Care Products Council on the Draft Final Amended Report on of 2,4-Diaminophenoxyethanol HCl and 2,4-Diaminophenoxyethanol Sulfate. The comments are primarily editorial in nature and will be addressed following the March Panel meeting.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: March 3, 2025

SUBJECT: Draft Final Amended Report: Amended Safety Assessment of 2,4-Diaminophenoxyethanol HCl and 2,4-Diaminophenoxyethanol Sulfate as Used in Cosmetics (draft prepared for the March 13-14, 2025 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft final amended report, Amended Safety Assessment of 2,4-Diaminophenoxyethanol HCl and 2,4-Diaminophenoxyethanol Sulfate as Used in Cosmetics.

Key Issues

Cosmetic Use – Although the description of MoCRA in the Cosmetic Use section is better, it is still not very clear. The report currently states: "As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was terminated in 2023, and as of 2024, manufacturers and processors have been mandated to register and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses, which are exempt from MoCRA reporting for most cosmetic product categories. However, to utilize the exemption, the small business must not sell eye area products, injected products, internal use products, or products that alter appearance for more than 24 h."

We suggest the following changes (shown in red): "As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was ~~terminated~~ discontinued in 2023, and as of 2024, manufacturers and processors ~~have been mandated~~ are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-year period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. ~~However, to utilize the exemption, the small business must not sell~~ Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products are not included in this exemption."

Cosmetic Use; Summary – Since FDA includes eyelash and eyebrow dyes under the category hair coloring preparations, it would be helpful to specifically state the number of uses reported in eyelash and eyebrow dyes not just the number of uses in hair coloring preparations.

Discussion – The Discussion should also note that there are reports of these ingredients being used in eyebrow and eyelash dyes.

Additional Considerations

Cosmetic Use; Summary – With the addition of the RLD information, is the comparison to the 2006 data necessary? If it is left in, it should be clearer that the frequency of use described as "slightly changed" was a comparison of the 2006 VCRP data with the 2023 VCRP data.

Acute, Oral, old report summary- Is it necessary to state that the LD_{50} was for Diaminophenoxyethanol HCl and state that it was the chlorhydrate form?

Developmental and Reproductive Toxicity – In the gavage study in female rats, it should be made clear that the rats were treated on gestation days 6-19 (it currently says that they were assessed on gestation days 6-19).

Carcinogenicity – Since there was only one mouse study, "In oral carcinogenicity studies" should be revised to "In an oral carcinogenicity study".

Summary – The description of the EU cosmetic regulation and SCCS opinion should be revised to make it clear that the regulation uses the concentration (2%) considered safe by the SCCS, e.g., The regulation limits the final use concentration to 2% which is the concentration in hair dye products that the SCCS determined does not pose a risk to the health of the consumer, apart from its sensitizing potential.

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, MSES, Senior Scientific Analyst/Writer, CIR.
Date: March 3, 2025
Subject: Wave 2 - Safety Assessment of Copper Gluconate as Used in Cosmetics

Please find attached the comments provided by the Personal Care Products Council on the Draft Final Report on Copper Gluconate. The Panel should carefully consider the key comments concerning the Discussion section of the report and provide input. The remaining comments are primarily editorial in nature and will be addressed following the March Panel meeting.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: March 3, 2025

SUBJECT: Draft Final Report: Safety Assessment of Copper Gluconate as Used in Cosmetics (draft prepared for the March 13-14, 2025 meeting)

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

Key Issues

Cosmetic Use – Although the description of MoCRA in the Cosmetic Use section is better, it is still not very clear. The report currently states: "As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was terminated in 2023, and as of 2024, manufacturers and processors have been mandated to register and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses, which are exempt from MoCRA reporting for most cosmetic product categories. However, to utilize the exemption, the small business must not sell eye area products, injected products, internal use products, or products that alter appearance for more than 24 h."

We suggest the following changes (shown in red): "As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was ~~terminated~~ discontinued in 2023, and as of 2024, manufacturers and processors ~~have been mandated~~ are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-year period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. ~~However, to utilize the exemption, the small business must not sell~~ Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products are not included in this exemption."

Discussion - The tumor promotion studies found changes in gene expression and possible preneoplastic lesions. They did not report "carcinogenic effects" as stated in the Discussion.

Dietary concentrations used in oral studies should not be compared to concentrations used in cosmetic products (doses should be compared as was done in the Exposure Assessment section).

In the Abstract and Discussion, it is not clear what is meant by the heavy metal limitations set by EPA as they are not mentioned elsewhere in the report.

Additional Considerations

Exposure Assessment – For skin surface exposure, it would be helpful to state that the values are for copper.

Summary – The mouthwash product was removed from the Exposure Assessment section. It should also be removed from the Discussion.

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From Jinqiu Zhu, Ph.D., DABT, ERT, DCST, CIR Toxicologist
Priya Cherian, M.S., Senior Scientific Analyst/Writer, CIR
Date: March 3, 2025
Subject: Response to comments on Octoxynols submitted by WVE

Enclosed are comments received from Women's Voices for the Earth (WVE) on Octoxynols (named *WVEcomments_Octoxynols_Wave2_032025* in the pdf). While the comments are dated February 24, 2025, they were sent to CIR via email in the evening of March 2, 2025. CIR values input from all stakeholders and the public; however, to ensure a thorough and timely response and to enhance the effectiveness of the Panel's safety assessment, CIR discourage delays in submission that may limit the time available for proper consideration and response. Timely submission of comments can facilitate a more productive and well-informed scientific discussion.

For the Panel's consideration, a table has been included herein listing the comments and a response from CIR staff. The Panel is requested to review WVE's comments and, if necessary, consider making further changes to the report based thereon.

WVE Comment	**CIR Staff Response**
A main reason this safety assessment was reopened was to explore the potential harm of octoxynols to vaginal mucous membranes. The RLD data detailed in the Cosmetic Use section indicates that there are currently marketed products containing octoxynols that may have vaginal mucous membrane exposure. New data has been added to the safety assessment of the adverse effects of octoxynols on vaginal tissue. **Yet the current draft of the summary section inexplicably omits most of this important information**. We strongly encourage significant attention to this concern in both the discussion and conclusion.	According to the CIR report format, results presented in the Summary section should be concise. For instance, under the Mucous Membrane Irritation Studies section, multiple study details are included. However, in the Summary section, the data are condensed into a single sentence: "An octoxynol (tested at 1%) resulted in cytotoxicity to **oral tissue models** when used as a positive control in 2 assays."
The safety assessment includes some data on nonoxynols as relevant read across sources, but omits any reference to the FDA required labeling of vaginal spermicides containing nonoxynol-9 implemented in 2007. This labeling requires warning language to "*advise consumers that use of vaginal contraceptives and spermicides containing N9 can irritate the vagina and rectum and may increase the risk of getting the AIDS virus (HIV) from an infected partner*." (It is worth noting that the FDA weighed these risks against the benefits of pregnancy prevention that N9 provides. No such benefits are intended of course for vaginal cosmetics containing these ingredients.) **Information on the increased risk of sexually transmitted diseases from vaginal exposure to octoxynols from cosmetics should be included in the safety assessment and discussed by the Expert Panel.**	It is unclear why these comments were raised. However, it should be noted the following statement under the Non-Cosmetic section has been included in the Draft Amended Report, which the Panel is about to review at the March meeting: "In 2002 (67FR31123), the FDA issued a final rule stating that the use of Octoxynol-9 in over-the counter (OTC) drugs is not deemed generally recognized as safe or effective (GRASE), and therefore that any drug product containing Octoxynol-9 labeled for OTC use as a vaginal contraceptive or spermicide will be considered misbranded (and will require a drug application), which was reiterated in 21CFR310.545. Additionally, **21CFR201.325 states that when nonoxynol-9 is used in OTC vaginal contraceptives and spermicides, labeling requirements include a warning that the products do not protect against human immunodeficiency virus (HIV) or other sexually transmitted diseases, of the potential for vaginal/ rectal irritation, and of potentially increased risk of HIV transmission from an infected partner**." (See pdf page 31 at https://www.cir-safety.org/sites/default/files/Octoxynols_1.pdf)
Similarly, the draft safety assessment omits any mention that the FDA issued a final rule stating that OTC vaginal contraceptive products containing Octoxynol-9 are not generally recognized as safe and effective. This ruling was in response to a lack of safety data from manufacturers, and resulted in the removal of all octoxynol-9 containing vaginal contraceptives from the market. The Expert Panel should determine if there is any new safety data sufficient to recognize vaginal cosmetic products containing Octoxynol-9 as safe.	Notably, the quoted statement above also clarifies that "In 2002 (67FR31123), the FDA issued a final rule stating that the use of **Octoxynol-9 in over-the counter (OTC) drugs is not deemed generally recognized as safe or effective (GRASE)**, and therefore that any drug product containing Octoxynol-9 labeled for OTC use as a vaginal contraceptive or spermicide will be considered misbranded (and will require a drug application), which was reiterated in 21CFR310.545."

WVE Comment	CIR Staff Response
Data on the spermicidal potency of Octoxynol-9 (Furuse et.al. 1983) that was included in the 2004 safety assessment was omitted from the current draft of the safety assessment. (The effective concentration of Octoxynol-9 for totally immobilizing all spermatozoa (human) within 20 seconds in vitro was just 0.24 mg/ml.). **Given that vaginal cleansing cosmetics are commonly used immediately before and/or after sex, the potential adverse impacts on sperm and fertility should be discussed in the safety assessment.**	In the CIR 2004 report, the following data were included: "Furuse, Ishizeki, and Iwahara (1983) reported that the effective concentration of **Nonoxynol-9** for totally immobilizing all spermatozoa (human) within 20 s in vitro was 0.24 mg/ml." It is important to note that these data pertain to Nonoxynol-9, not Octoxynol-9.
The safety assessment includes outdated language on inhalation potential (excerpted from the 2004 safety assessment). The current draft claims that all particles from hair sprays are too big to be inhaled thus dismissing any potential for inhalation in the exposure assessment section. This is inconsistent with the CIR inhalation boilerplate language being developed which indicates that some cosmetic sprays contain larger percentages of inhalable particles.	CIR inhalation resource document as well as the inhalation boilerplate (BP) language have been revised and are scheduled for review by the Panel at the upcoming March meeting (Please see the relevant revisions at https://www.cir-safety.org/sites/default/files/Admin_Inhalation_032025.pdf). Once the inhalation documents are finalized, the corresponding language will be updated accordingly.
The 2025 version of the safety assessment is considerably shorter than the last published version from 2004 and contains a great deal less information. It is unclear why so much research on octoxynols previously considered by the CIR Expert Panel was omitted from this newest version.	In the re-opened draft amended report, the focus is on newly identified data since the last finalization, while italicized summaries of data from previous reports are provided for the Panel's reference in their safety assessment process. Generally, revised reports do not incorporate all information from previous CIR reports.
Starting at least on page 38 – the citations are misnumbered. For example, the sentence on bovine ocular damage on page 38 cites reference 23 – but the actual paper is reference 22. The sentence on vaginal cleansing films claims to be from Reference 24, but is actually from Reference 23. It appears at some point in the draft the citations were misnumbered by one. (I did not check them all.) All citations in the draft assessment should be checked for accuracy for the next version.	This draft amended report was last tabled at the December 2023 meeting when Endnote was used as the citation software. However, it has now been transferred to RefWorks, which may have caused some transition issues that could not be fixed prior to the submission of this report. CIR staff will carefully review the citations to identify and correct any errors prior to the next iteration.

February 24, 2025

Re: Comments on the Amended Safety Assessment of Octoxynols as Used in Cosmetics

To the CIR:

The following comments are submitted on behalf of Women's Voices for the Earth.

We have a number of concerns with the current draft of the Amended Safety Assessment of Octoxynols:

- A main reason this safety assessment was reopened was to explore the potential harm of octoxynols to vaginal mucous membranes. The RLD data detailed in the Cosmetic Use section indicates that there are currently marketed products containing octoxynols that may have vaginal mucous membrane exposure. New data has been added to the safety assessment of the adverse effects of octoxynols on vaginal tissue. **Yet the current draft of the summary section inexplicably omits most of this important information**. We strongly encourage significant attention to this concern in both the discussion and conclusion.

- The safety assessment includes some data on nonoxynols as relevant read across sources, but omits any reference to the FDA required labeling of vaginal spermicides containing nonoxynol-9 implemented in 2007. This labeling requires warning language to "*advise consumers that use of vaginal contraceptives and spermicides containing N9 can irritate the vagina and rectum and may increase the risk of getting the AIDS virus (HIV) from an infected partner*."[1] (It is worth noting that the FDA weighed these risks against the benefits of pregnancy prevention that N9 provides. No such benefits are intended of course for vaginal cosmetics containing these ingredients.) **Information on the increased risk of sexually transmitted diseases from vaginal exposure to octoxynols from cosmetics should be included in the safety assessment and discussed by the Expert panel.**

- **Similarly the draft safety assessment omits any mention that the FDA issued a final rule stating that OTC vaginal contraceptive products containing Octoxynol-9 are not generally recognized as safe and effective.** This ruling was in response to a lack of safety data from manufacturers, and resulted in the removal of all octoxynol-9 containing vaginal contraceptives from the market. The Expert Panel should determine if there is any new

[1] https://www.federalregister.gov/documents/2007/12/19/07-6111/over-the-counter-vaginal-contraceptive-and-spermicide-drug-products-containing-nonoxynol-9-required

safety data sufficient to recognize vaginal cosmetic products containing octoxynol-9 as safe.[2]

- Data on the spermicidal potency of Octoxynol-9 (Furuse et.al. 1983) that was included in the 2004 safety assessment was omitted from the current draft of the safety assessment. (The effective concentration of Octoxynol-9 for totally immobilizing all spermatozoa (human) within 20 seconds in vitro was just 0.24 mg/ml.). **Given that vaginal cleansing cosmetics are commonly used immediately before and/or after sex, the potential adverse impacts on sperm and fertility should be discussed in the safety assessment.**

- **The safety assessment includes outdated language on inhalation potential (excerpted from the 2004 safety assessment).** The current draft claims that all particles from hair sprays are too big to be inhaled thus dismissing any potential for inhalation in the exposure assessment section. This is inconsistent with the CIR inhalation boilerplate language being developed which indicates that some cosmetic sprays contain larger percentages of inhalable particles.

- **The 2025 version of the safety assessment is considerably shorter than the last published version from 2004 and contains a great deal less information.** It is unclear why so much research on octoxynols previously considered by the CIR Expert Panel was omitted from this newest version.

- **Starting at least on page 38 – the citations are misnumbered.** For example, the sentence on bovine ocular damage on page 38 cites reference 23 – but the actual paper is reference 22. The sentence on vaginal cleansing films claims to be from Reference 24, but is actually from Reference 23. It appears at some point in the draft the citations were misnumbered by one. (I did not check them all.) All citations in the draft assessment should be checked for accuracy for the next version.

Thank you for your consideration of these comments.

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

[2] https://www.govinfo.gov/content/pkg/FR-2002-05-09/pdf/02-11511.pdf

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, MSES, Senior Scientific Analyst/Writer, CIR
Date: March 3, 2025
Subject: Wave 2 - Amended Safety Assessment of *p*-Phenylenediamine, *p*-Phenylenediamine HCl, and *p*-Phenylenediamine Sulfate as Used in Cosmetics

Please find attached the comments provided by the Personal Care Products Council on the Draft Final Amended Report on of *p*-Phenylenediamine, *p*-Phenylenediamine HCl, and *p*-Phenylenediamine Sulfate. Please note that the only comment made addresses the updated wording now included in the Cosmetic Use section. Since this key comment occurred in all the comments submitted by the Council, it will be addressed accordingly following Panel discussion at the meeting.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: March 3, 2025

SUBJECT: Draft Final Amended Report: Amended Safety Assessment of p-Phenylenediamine, p-Phenylenediamine HCl and p-Phenylenediamine Sulfate as Used in Cosmetics (draft prepared for the March 13-14, 2025 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft final amended report, Amended Safety Assessment of p-Phenylenediamine, p-Phenylenediamine HCl and p-Phenylenediamine Sulfate as Used in Cosmetics.

Key Issues

Cosmetic Use – Although the description of MoCRA in the Cosmetic Use section is better, it is still not very clear. The report currently states: "As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was terminated in 2023, and as of 2024, manufacturers and processors have been mandated to register and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses, which are exempt from MoCRA reporting for most cosmetic product categories. However, to utilize the exemption, the small business must not sell eye area products, injected products, internal use products, or products that alter appearance for more than 24 h."

We suggest the following changes (shown in red): "As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was ~~terminated~~ discontinued in 2023, and as of 2024, manufacturers and processors ~~have been mandated~~ are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-year period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. ~~However, to utilize the exemption, the small business must not sell~~ Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products are not included in this exemption."

Cosmetic Ingredient Review

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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
Date: March 3, 2025
Subject: Wave 2 - Amended Safety Assessment of Propylene Carbonate as Used in Cosmetics

Enclosed are comments from Personal Care Products Council on the Draft Tentative Amended Report on Propylene Carbonate. Of note is information regarding UV absorption and a suggestion to the Panel to rely on the 13-wk inhalation study performed in rats to support the inhalation safety of this ingredient in the Discussion, rather than using boilerplate language. In addition, it should be noted that Council suggested including a notation in the Introduction and Summary stating that propylene glycol was previously reviewed by the Panel and considered safe.

The Panel should consider all submitted comments and provide feedback on whether the suggested edits should be made.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: March 3, 2025

SUBJECT: Draft Tentative Amended Report: Amended Safety Assessment of Propylene Carbonate as Used in Cosmetics (draft prepared for the March 13-14, 2025 meeting)

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

Key Issues

Propylene Carbonate is included in a list of UV cutoffs (the wavelength at which the solvent absorbance in a 1 cm path length cell is equal to 1 AU (absorbance unit) using water in the reference cell) for solvents https://macro.lsu.edu/HowTo/solvents/UV%20Cutoff.htm. The UV cutoff for Propylene Carbonate is listed as 220 nm.

The following statement is from a paper that developed an analytical method for Propylene Carbonate in pharmaceuticals: "Unfortunately, PC [Propylene Carbonate} has two major analytical disadvantages. Firstly, it is transparent in the UV region [16] and secondly, it lacks chromophore functional groups, making spectrophotometric approaches useless [17]". The analytical method described in the paper required a derivatization step to measure Propylene Carbonate.

Reference:
https://www.sciencedirect.com/science/article/abs/pii/S0039914016300212#:~:text=Unfortunately%2C%20PC%20has%20two%20major,of%20different%20analytes%20%5B22%5D

Grizić D, Heimer P, Vranić E, et al. 2016. Propylene carbonate quantification by its derivative 3,5-diacetyl-1,4-dihydro-2,6-lutidine. Talanta 151(1): 75-82.

Perhaps this information will help address the Expert Panel's concerns regarding UV absorption.

Cosmetic Use – Although the description of MoCRA in the Cosmetic Use section is better, it is still not very clear. The report currently states: "As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was terminated in 2023, and as of 2024, manufacturers and processors have been mandated to register and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses, which are exempt from MoCRA reporting for most cosmetic product categories. However, to utilize the exemption, the small business must not sell eye area products, injected products, internal use products, or products that alter appearance for more than 24 h."

We suggest the following changes (shown in red): "As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was ~~terminated~~ discontinued in 2023, and as of 2024, manufacturers and processors ~~have been mandated~~ are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-year period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. ~~However, to utilize the exemption, the small business must not sell~~ Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products are not included in this exemption."

Dermal Irritation and Sensitization, old report summary – Since irritation is an endpoint of concern, it would be helpful to have additional information on the studies of cosmetic products or gels containing 0.54-20%. The current draft says that products containing 0.54-20% Propylene Carbonate were "moderately irritating [to] human skin" – which implies that all the products were moderately irritating. This is not true. The original CIR report says that the products were "at most moderately irritating" which means some products were not moderately irritating. Based on the table in the original CIR report, some of the products were not irritating, and the irritation potential of some products was not stated.

Discussion – Rather than using boilerplate language, the Discussion should rely on the 13-week study (6 hours/day, 5 days/week) in rats (inhalation systemic NOAEC 1000 mg/m^3, inhalation local NOAEC 100 mg/m^3) to support the inhalation safety of this ingredient.

<u>Additional Considerations</u>

Introduction; Summary – In the Introduction and Summary, it would be helpful to note that the metabolite of Propylene Carbonate, propylene glycol has been reviewed by CIR and has a safe when formulated to be non-irritating conclusion.

Summary – The Summary should also include the local inhalation NOAEC of 100 mg/m^3.