Data Supplement

Priorities RAWG

Hair Dye Epi ADMIN

2-Bromo-2-Nitropropane-1,3-Diol

Cocoyl Hydrolyzed Collagens

Oxyquinoline and Oxyquinoline Sulfate

Paeonia suffruticosa

Propylene Carbonate

Pyrogallol

Tetrabromophenol Blue

EXPERT PANEL MEETING

June 9-10, 2025

Commitment & Credibility since 1976

Memorandum

To: Read-Across Working-Group (RAWG) Members of the Expert Panel for Cosmetic Ingredient Safety
From: Bart Heldreth, PhD, Executive Director, CIR.
Date: May 30, 2025
Subject: Wave 2 – Draft 2026 Priorities

Please find attached herein the comments and concentration of use data provided by the Personal Care Products Council regarding the Draft 2026 Priorities. The comments and data speak to priorities inclusion criteria for Alpha-Isomethyl Ionone, Tetramethyl Acetyloctahydronaphthalenes, Octocrylene, Ethyl Trimethylbenzoyl Phenylphosphinate, and Bis-Trimethylbenzoyl Phenylphosphine Oxide.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council (PCPC)

DATE: May 21, 2025

SUBJECT: Concentration of Use by FDA Product Category

Alpha-Isomethyl Ionone was included in a concentration of use survey with a request for only non-fragrance uses (in this case fragrance refers to the function in the product, rather than a type of product category). No non-fragrance uses were reported.

Results for the non-fragrance uses for Tetramethyl Acetyloctahydronaphthalenes, the non-sunscreen uses of Octocrylene, and the results for Ethyl Trimethylbenzoyl Phenylphosphinate Bis-Trimethylbenzoyl Phenylphosphine Oxide are also attached.

Concentration of Use by FDA Product Category[1]

Ethyl Trimethylbenzoyl Phenylphosphinate
Bis-Trimethylbenzoyl Phenylphosphine Oxide

Ingredient	Product Category	Maximum Concentration of Use
Ethyl Trimethylbenzoyl Phenyl Phosphinate	Nail polish and enamel	4-6.2%
Ethyl Trimethylbenzoyl Phenyl Phosphinate	Other manicuring preparation	0.25%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2025
Table prepared: May 21, 2025

[1] The new FDA cosmetic product categories under MoCRA were used for this survey.

Concentration of Use by FDA Product Category[1]

Etocrylene and Octocrylene*

Ingredient	Product Category	Maximum Concentration of Use
Etocrylene	Basecoats and undercoats (manicuring preparations)	0.5%
Etocrylene	Nail polish and enamel	10%
Etocrylene	Suntan products (not spray)	3%
Etocrylene	Suntan products (spray) Aerosol	 3%
Octocrylene	Nail polish and enamel	0.5%
Octocrylene	Other manicuring preparations	0.2%

*In the United States, 10% is the maximum concentration of Octocrylene permitted for use in sunscreen products. The concentrations of Octocrylene included in this table are for non-sunscreen uses.

Information collected in 2025
Table prepared: May 21, 2025

[1] The new FDA cosmetic product categories under MoCRA were used for this survey.

Concentration of Use by FDA Product Category[1]

Tetramethyl Acetyloctahydronaphthalenes – non fragrance uses

Product Category	Maximum Concentration of Use
Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.075%
Face and neck products (not spray) Leave-on	 0.09%

For comparison IFRA standard for OTNE (CAS No. 54464-57-2)
https://ifrafragrance.org/standards/IFRA_STD48_0112.pdf :

Category 9: Products with body and hand exposure, primarily rinse off 2.4%
Category 5b: Face moisturizer products applied to the face using the hands (palms), primarily leave on 0.56%

Information collected in 2025
Table prepared: May 21, 2025

[1] The new FDA cosmetic product categories under MoCRA were used for this survey.

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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
Date: May 30, 2025
Subject: Response to comments on Hair Dye Epi Resource Document submitted by WVE

Enclosed are comments received from Women's Voices for the Earth (WVE) on the Hair Dye Epidemiology Resource Document, dated May 28, 2025 (identified as *WVEcomments_HairDyeDocument_Wave2_062025*). In the comments, WVE acknowledges the improvements made to the document, particularly the addition of newly published studies and enhanced clarity. However, they express concern about the broad conclusion that the current epidemiological data do not support a causal relationship between personal hair dye use and cancer. While WVE recognizes that this conclusion may be scientifically accurate, they argue that it lacks nuance, given that some studies cited in the report suggest increased risks for certain cancer types within specific populations. They recommend CIR to consider providing precautionary guidance for vulnerable groups–for example, suggesting that black women with a family history of breast cancer consider reducing their exposure to permanent hair dye–and to further clarify the intended purpose of this document.

While WVE draws an analogy between hair dye exposure and ultraviolet (UV) radiation to highlight the supposed rarity of causal determinations by authoritative bodies, this comparison is misleading. Unlike the epidemiological data on personal hair dye use, which remains inconclusive and limited by confounders and study heterogeneity, the link between UV exposure and cancer–specifically skin cancers such as malignant melanoma and squamous cell carcinoma–has been firmly established. The International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) has classified solar radiation as a **Group 1** carcinogen, indicating sufficient evidence in humans for its carcinogenicity. As such, UV exposure represents a well-substantiated exception rather than a typical case of scientific uncertainty. Therefore, equating the state of evidence on personal hair dye use with that of UV exposure undermines the critical differences in data robustness, disease specificity, and the degree of global scientific consensus. Small amounts of UV are essential for the production of vitamin D in people, yet overexposure may result in acute and chronic health effects on the skin, eye and immune system.

Furthermore, as stated in the Introduction section of the Resource Document (see pdf page 61 – 62 at https://www.cir-safety.org/sites/default/files/ADMIN_HairDyeEpi_0.pdf), the **IARC** of WHO *concluded that while animal studies provided limited evidence for the carcinogenicity of hair colorants, the overall data lacked sufficient quality, consistency, and statistical power to determine a causal relationship between* ***personal hair dye use*** *and cancer. Due to insufficient evidence from human studies, IARC considers personal hair dye use "****not classifiable as to its carcinogenicity to humans"*** *(classified as* ***Group 3****). The working group also evaluated occupational exposure among hairdressers, barbers, and beauticians, who are likely to experience more frequent and prolonged exposure to hair dyes than the general population. Based on limited evidence of an increased risk of bladder cancer* ***among hairdressers and barbers****, IARC classified* ***occupational exposure to hair dyes*** *as "probably carcinogenic to humans" (classified as* ***Group 2A****). Evidence regarding other cancer types, however, was considered* ***inconsistent or inadequate****… However, the evaluation of* ***occupational*** *safety falls* ***outside the scope*** *of the Panel's review… To date, the* ***US FDA*** *considers* ***no reliable evidence has demonstrated a link*** *between cancer and the use of currently marketed coal-tar hair dyes.*

In the safety checklist for coal-tar hair dye use provided by the U.S. FDA (https://www.fda.gov/cosmetics/cosmetic-products/hair-dyes#checklist), several protective measures are recommended to minimize exposure, such as: "Wear gloves when applying hair dye;" "Rinse your scalp well with water after using hair dye;" "Do not scratch or brush your scalp for three days before using hair dyes;" "Do not dye or relax your hair if your scalp is irritated, sunburned, or damaged;" and "Wait at least 14 days after bleaching, relaxing, or perming your hair before using dye." However, these precautions pertain to safe product use and are not relevant to the review of epidemiological data; therefore, they are not included in the Resource Document.

It is important to note that hair dye formulations have evolved over time, with ongoing efforts to monitor and mitigate potential risks associated with their use. These formulations also vary across regions; however, specific formulation information was not provided, and regional differences were not evaluated in the epidemiological studies included in the Resource Document. The carcinogenic potential of individual hair dye ingredients under review remains a key concern for the Panel. When necessary, CIR should conduct ingredient-specific risk assessments using the margin of exposure (MOE) approach.

Regarding the observed increased risk of specific types of cancer in certain populations associated with particular patterns of hair dye use, as discussed in the Resource Document (see pdf page 74 at https://www.cir-safety.org/sites/default/files/ADMIN_HairDyeEpi_0.pdf), *while several large-scale cohort studies have generally found no strong evidence linking hair dye use to an increased overall cancer risk, stratified analyses suggest that certain subgroups, hair dye types or shades, and specific exposure patterns may be associated with increased risks for cancer subtypes. For instance, one study reported an elevated risk of breast cancer associated with the use of permanent hair dye, especially among black women. However, this finding should be interpreted cautiously and not generalized to the broader population due to several limitations, including selection bias, lack of age-related behavioral patterns adjustment, and unaddressed confounding from EDC exposure, as well as social and cultural factors.* ***Well-designed studies with adequate statistical power are needed to robustly evaluate the possibility of differences by race and tumor subtype***.

The Panel is requested to review the comments submitted by WVE and, if deemed necessary, consider revising the conclusion of the Resource Document or offering precautionary guidance for certain vulnerable populations to reduce their exposure to permanent hair dye.

May 28, 2025

Re: Comments on the Hair Dye Epidemiology Document

To the CIR:

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

We appreciate the updates and improved clarity of the Hair Dye Epidemiology document since we last commented on a draft. We were glad to see new studies being added to the document as they are published. We see value in this being a living document that learns from and is improved by new research.

We still have a concern with the overall broad nature of the document's conclusion:

> *"CONCLUSION*
>
> *The Expert Panel for Cosmetic Ingredient Safety determined that the available hair dye epidemiology data, as summarized in the current document, do not provide sufficient evidence to support a causal relationship between personal hair dye use and cancer."*

As I have mentioned in earlier comments – it is exceedingly rare for any authoritative body to determine a causal relationship between any one kind of exposure and "cancer" in general. More commonly, certain exposures are associated with increased risks of certain cancers – leading to helpful and practical recommendations to reduce the risk of those types of cancer. Ideally, the CIR Hair Dye Epidemiology document could do the same, given that it does document highly rated studies showing increased risk of specific types of cancer in specific populations associated with hair dye use. Instead, the overly broad conclusion of "no causal relationship with cancer" remains unchanged with every updated draft.

While the broad conclusion may be scientifically accurate, the choice to use it is concerning from the standpoint of optics and the CIR's reputation.

Imagine if the American Suntanning Association (a trade association of sunbed salons) published an epidemiology review on UV exposure and cancer. It would include a number of studies showing **decreased** risk of breast cancer, prostate cancer, colorectal cancer associated with UV exposure (largely linked to the benefits of Vitamin D production etc.) There are even metastudies showing a small but significant overall **decreased risk of all-cancer death** from lifetime UV exposure. And, of course, buried in a long list of studies, it would also have to include quite a few studies showing **significantly increased risk of skin cancers from UV exposure**. An overall broad conclusion however – most accurately - would be to conclude that:

> *"the available UV exposure epidemiology data do not provide sufficient evidence to support a causal relationship between UV exposure and cancer."*

Obviously, this overall conclusion, while scientifically accurate, would be misleading, highly controversial and incredibly unhelpful to public health at large. And it would be a discredit to the American Suntanning Association, who would be seen as generating a pseudoscientific report, intentionally crafted to result in a conclusion that benefits the sunbed tanning industry.

It's not a perfect analogy to the CIR's Hair Dye Epidemiology document, but I hope it provides some perspective. The CIR Expert Panel should not risk giving the impression that the conclusion of this report was predetermined by the PCPC to support the hair dye industry.

Instead, the conclusion of the hair dye epidemiology report could include more nuance about the current state of research, and provide helpful recommendations for people looking to proactively reduce their risks. For example, based on what we know now, does the CIR Expert Panel believe that black women with a family history of breast cancer should reduce their exposure to permanent hair dye as a precautionary preventative measure? Or as the last paragraph of the Discussion section seems to imply, does the CIR recommend they should they wait until studies can be replicated before taking action (and accept the increased breast cancer risk of ongoing exposure if future studies confirm the current results)?

The CIR should decide what the goals and purposes of this document are. Is it merely an internal academic exercise to compile the relevant research on the subject of hair dyes and cancer? Is it a document intended to publicly "prove" the assumed safety of hair dye use to support the industry? Or is it a document intended to educate both hair dye users and manufacturers, which could be useful to promote improved public health and the development of safer products?

Thank you for your consideration of these comments.

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

Cosmetic Ingredient Review

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To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Thushara Diyabalanage, Ph.D., Scientific Analyst/Writer, CIR
Date: May 30, 2025
Subject: Wave 2 - Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol

Please find the attached comments of the Personal Care Products Council (*PCPCcomments_Wave2_2-Bromo-2-Nitopropane-1,3-Diol_062025*) on the Draft Amended Report on the Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol. The comments are primarily editorial in nature and will be addressed following the June Panel meeting.

Also, please find attached comments provided by the Women's Voices for the Earth on the Draft Amended Report on 2-Bromo-2-Nitropropane-1,3-Diol (*WVEcomments_Wave2_2-Bromo-2-Nitropropane_1,3-Diol_062025*).

At the September 2024 meeting, the Panel decided to reopen the assessment of this ingredient, in part due to concerns about formaldehyde release and potential *N*-nitrosamine formation. These concerns were reiterated by WVE in their comments, where they specifically noted the limited availability of carcinogenicity data. They further suggested 2-Bromo-2-Nitropropane-1,3-Diol should be limited to use in rinse-off products, considering the detection of formaldehyde in an in vitro skin penetration study (reference 19 of the current report; López-Sánchez et al., 2021).

It should be noted that the margin of exposure (MOE) to free formaldehyde from personal care products containing formaldehyde-donor (FD) preservatives has been evaluated. A 2023 study[1] provided a quantitative cancer risk assessment of formaldehyde in FD-containing personal care products. The worst-case consumer exposure to formaldehyde was estimated to be 0.007 µg/kg/d, which represents less than 1.0×10^{-6} % of background level endogenous formaldehyde (878 - 1310 mg/kg/d). This estimate was based on the aggregate daily application of personal care products at 17.4 g/d under intended use conditions and a fraction of free formaldehyde concentration in personal care products at 0.3 ppm, considering both dermal and inhalation exposure routes. By comparing the estimated consumer exposure of 0.007 µg/kg/d to the benchmark dose lower confidence limit (BMDL) of 2.52 mg/kg/d, derived from a 104-wk carcinogenicity study in rats exposed to formaldehyde, the MOE for the worst-case scenario was calculated to be 360,000. Thus, the authors concluded that the cancer risk from formaldehyde to consumers using FD-containing personal care products is negligible.

WVE further recommended the inclusion of a 2023 study that detected nine *N*-nitrosamines in three marketed cosmetic products containing 2-Bromo-2-Nitropropane-1,3-Diol as an ingredient. It is worth noting that in the 2006 re-review, the Panel reaffirmed the conclusion from the 1980 assessment, stating that "2-Bromo-2-Nitropropane-1,3-Diol to be safe as a cosmetic ingredient at concentrations up to and including 0.1% **except** under circumstances where its action with amines or amides can result in the formation of nitrosamines or nitrosamides." According to the Council's 2023 survey, the maximum use concentration of 2-Bromo-2-Nitropropane-1,3-Diol in cosmetics has decreased to 0.05 and 0.026% for leave-on and rinse-off products, respectively.

The Panel is requested to review the comments submitted by WVE. Potential points to considered for addition to the Discussion section include: addressing the concerns expressed regarding carcinogenicity; possible accumulation of formaldehyde after prolonged exposure; and the presence of N-nitrosamine in some cosmetic products that contain 2-Bromo-2-Nitropropane-1,3-Diol.

Reference

1. Kim ST, Shao K, Oleschkewitz C, Hamilton R. Margin of exposure to free formaldehyde in personal care products containing formaldehyde-donor preservatives: Evidence for consumer safety. Regul Toxicol Pharmacol. 2023;145:105519.

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: May 27, 2025

SUBJECT: Draft Amended Report: Amended Safety Assessment 2-Bromo-2-Nitropropane-1,3-Diol as Used in Cosmetics (draft prepared for the June 9-10, 2025 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft amended report, Amended Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol as Used in Cosmetics.

Key Issues
It is not clear why the sensitization mechanism paper (citation below) presented in the original re-review summary table considered during the Sept 30-Oct 1, 2024 meeting is not included in this draft of the CIR report.

Kireche M, Peiffer J-L, Antonios D, et al. Evidence for chemical and cellular reactivities of the formaldehyde releaser bronopol, independent of formaldehyde release., J. Chem Res Toxicol. 2011, 24, (12), 215-2128.

As nitrosamine formation is a concern of the Expert Panel, it is not clear why these older papers (citations and abstracts below) do not appear to have been included in a CIR report on 2-Bromo-2-Nitropropane-1,3-Diol.

Int J Cosmet Sci1984 Oct;6(5):241-7. doi: 10.1111/j.1467-2494.1984.tb00381.x.

Study of the fate of Bronopol and the effects of antioxidants on N-nitrosamine formation in shampoos and skin creams

P C Dunnett [1], G M Telling

Affiliation

- [1]Uniliver Research Laboratory, Colworth House, Sharnbrook, Beds, MK44 1LQ, U.K.
- PMID: 19467116

Abstract

Synopsis The role of antioxidants in preventing nitrosamine (N-nitroso diethanolamine) formation in shampoos and skin creams and the levels of Bronopol (2-bromo, 2-nitropropane-1, 3-diol) addition in relation to the resultant levels of N-nitroso compounds have been studied. The addition of 0.05% BHT, alpha-tocopherol or ascorbate was effective in preventing nitrosamine formation (limit of determination: 2.5 mug kg(-1)) in products preserved with 0.01% Bronopol. At 0.05% Bronopol, 0.2% of all three antioxidants was effective in preventing nitrosamine formation but at 0.1% Bronopol only alpha-tocopherol was effective. Levels of Bronopol found in shampoo formulations stored for 2 weeks at 37 degrees C with initial concentrations of 0.005-0.1% were reduced by 64-86%, independent of the initial concentration. The levels in skin creams stored for extended periods at ambient temperature with 0.01% Bronopol initially were reduced by, on average, 60%. High nitrite levels (NO(2) (-)) were found in formulations containing 0.01% Bronopol but no antioxidants (200-250 mg kg(-1)). Detected levels of nitrite in skin cream formulations were greater than could be formed by stoichiometric decomposition of Bronopol. In formulations with both Bronopol and antioxidants the levels of nitrite were considerably reduced. When alpha-tocopherol rather than BHT or ascorbate was the antioxidant then the nitrite levels were appreciably higher but formation of N-nitroso diethanolamine was no greater. High nitrite levels correlated with the formation of detectable levels of N-nitroso compounds in the absence of antioxidants.

IARC Sci Pub 1991:(105):238-41.

N-nitrosoalkanolamines in cosmetics

G Eisenbrand [1], M Blankart, H Sommer, B Weber

Affiliation

- [1]Department of Food Chemistry and Environmental Toxicology, University of Kaiserslautern, Germany.

- PMID: 1855860

Abstract

A method has been developed for the determination of the N-nitrosoalkanolamines, N-nitrosodiethanolamine (NDELA) and N-nitrosobis(2-hydroxypropyl)amine (NDHPA) in cosmetics. In model systems, we studied nitrosation of the most relevant precursors by NaNO2, by the preservatives Bronopol and Bronidox and by nitric oxides. Secondary amines were most rapidly nitrosated, and Bronopol, Bronidox and atmospheric nitric oxides appeared to be the most relevant nitrosating agents. In order to remove the most important sources of contamination, the Federal Health Office issued an official recommendation to producers to avoid use of secondary amines in cosmetics (March, 1987). Analysis of cosmetics taken from the German market 6-18 months later showed that only 19/126 samples were contaminated with NDELA (12-235 micrograms/kg or NDHPA (40-215 micrograms/kg). The results reflect a strong downward trend in contamination.

It looks like the NICNAS assessment relied heavily on the EPA reregistration document for references. For those studies NICNAS cited to EPA, it would be helpful to go directly to the EPA reregistration document at https://archive.epa.gov/pesticides/reregistration/web/pdf/2770red.pdf and cite it, rather than citing the tertiary document NICNAS document which cites the secondary EPA reference (which relies on unpublished industry data).

Genotoxicity, In Vitro – The description of the V79/HPRT-test only describes cytotoxicity results. Checking the ECHA dossier, it says the results (mutant frequencies) were positive without metabolic activation and equivocal with metabolic activation. The description in the CIR report needs to be corrected.

Additional Considerations

Introduction – Although it is a trade name, Bronopol is another name commonly used for this ingredient. It would be helpful to state this in the Introduction of this report.

Cosmetic Use; Summary; Table 2 – It would be helpful to note that the PCPC survey completed in 2023 was by FDA VCRP cosmetic product categories, while the survey completed in 2025 was by FDA MoCRA cosmetic product categories, e.g., the survey completed in 2025 included the disposable wipes category, a category not included in the 2023 survey.

The limit for the use of 2-Bromo-2-Nitropropane-1,3-Diol for use in cosmetics in Europe should be included in the report (0.1%). It should also be noted that the Annex V listing for Bronopol says "Avoid formation of nitrosamines".

Non-Cosmetic Use – The 21CFR citations permit the use of ingredients in FDA regulated products. In the Non-Cosmetic Use section, it would be more appropriate to say that the uses are permitted, rather than saying "It is used" (unless there is another reference that confirms the use). For the non-FDA regulated uses, e.g., non-agricultural and agricultural pesticides, paints, please provide a reference instead of the FDA 21CFR citations.

Dermal Absorption – Please identify the receptor fluid used in the in vitro study (reference 19).
ADME, old report summary – Please revise: "used urine to identify the metabolites" to "identified metabolites in urine"

Acute, Oral old report summary – Please revise the following sentences: "Two samples of 2-Bromo-2-Nitropropane-1,3-Diol tested in rats reported LD_{50} values of 292 and 320 mg/kg. The oral LD_{50} for aqueous solution of th etest material the mice and rats were reported as 350 and 400 mg/kg." Samples are not really able to "report". Correct: "the test" "the mice and rats" should be "in mice and rats".

Acute, Inhalation, old report study – It would be helpful to know how many exposure concentrations were used in the 4-hour inhalation study for which the LC_{50} was 18 mg/m^3.

Please correct "diffuse reg lungs" ("reg" should probably be "red")

Irritation, Animal old report summary – Please correct: “moderately to severely irritation” (delete “ly” in “moderately” and “severely” and change “irritation” to “irritants”)

In the last paragraph of this section, what were the “severe toxic effects” observed in mice? Was only the skin examined?

Retrospective and Single or Multicenter Studies, old report summary – Please correct “law reactivity” (“law” should be “low”)

Summary – Please correct: “administered mouse” (should be “administered to mice”)
Units of mg/m^3 should be called concentrations rather than doses.

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May 28, 2025

Re: Comments on the Amended Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol as Used in Cosmetics

To the CIR:

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

1) A more robust discussion of carcinogenicity is needed in the Safety Assessment given that 2-Bromo-2-Nitropropane-1,3-Diol is a formaldehyde releaser and formaldehyde is a known carcinogen.
2) Results of a recent in-vitro skin penetration study suggest 2-Bromo-2-Nitropropane-1,3-Diol should be limited to rinse-off products due to formaldehyde exposure. This finding should be discussed in the Safety Assessment.
3) A relevant study (Schettino, 2023) which detected N-nitrosamines in cosmetic products containing 2-Bromo-2-Nitropropane-1,3-Diol at levels 10 -16 times higher than allowable safety levels should be added to the Safety Assessment.

1) <u>Carcinogenicity</u>

The release of formaldehyde by 2-Bromo-2-Nitropropane-1,3-Diol, and other similar preservatives like Quaternium-15, diazolidinyl urea, DMDM hydantoin is the main issue that has brought recent attention and concern to the safety of these ingredients. A prominent safety concern with formaldehyde exposure is that it is a known carcinogen. It seems, however, there is a dearth of data on the carcinogenicity of formaldehyde releasing preservatives. It is well past time for the CIR Expert panel to address the carcinogenicity concern and the data gap directly in the Safety Assessments of formaldehyde releasers.

In the current Amended Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol there is a very brief section on carcinogenicity referencing the 1980 CIR safety assessment. The 1980 CIR Safety Assessment includes just one reference source on carcinogenicity; the source is unpublished data of Boots Co. from 1978. (We noted that a second reference mentioned in the Safety Assessment, Bryce et.al. (1978) is actually a summary paper on 2-Bromo-2-Nitropropane-1,3-Diol which merely includes a short paragraph summarizing the very same Boots Co. 1978 data.) This data is outdated, not peer-reviewed, and was conducted well before formaldehyde was declared a carcinogen. Newer data on carcinogenicity is needed for 2-Bromo-2-Nitropropane-1,3-Diol, (and should be requested from manufacturers) especially given that more recent tests have determined evidence of both genotoxicity and clastogenicity.

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We have noted a similar lack of discussion of carcinogenicity in other CIR Safety Assessments of formaldehyde releasers. In fact, none of the CIR Safety Assessments of formaldehyde releasers: DMDM Hydantion, Imidazolidinyl Urea, Quaternium-15, or Diazolidinyl Urea even contain a section on carcinogenicity, and no mention is made of this data gap in any of their discussion sections. The CIR Expert Panel must address the issue of carcinogenicity of these ingredients going forward to meet current public health concerns.

2) 2-Bromo-2-Nitropropane-1,3-Diol should be limited to rinse-off products

A recent study on in-vitro skin penetration of 2-Bromo-2-Nitropropane-1,3-Diol concluded the following:

> *"Nonetheless, taking into account that formaldehyde was detected in the receptor chamber after a long exposure to bronopol or DMDM hydantoin it could be important to restrict the use of these preservers to formulations that would require short time exposure, i.e. rinse-off products, as bronidox."*
>
> Source: (CIR Reference 19): López-Sánchez L, Miralles P, Salvador A, Merino-Sanjuán M, Merino V. In vitro skin penetration of bronidox, bronopol and formaldehyde from cosmetics. Regul Toxicol Pharmacol. 2021;122:104888.

This recommendation should be discussed by the CIR Expert Panel and included in the CIR Assessment.

3) N-Nitrosamines in cosmetic products containing 2-Bromo-2-Nitropropane-1,3-Diol

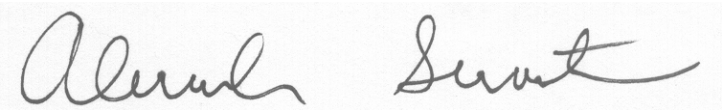
A 2023 study detected nine harmful N-nitrosamines in three currently marketed cosmetic products containing 2-Bromo-2-Nitropropane-1,3-Diol as an ingredient. Levels 10-18 times higher than the EU regulated safety level for certain N-Nitrosamines were found in all three products.

> *"The results obtained in the aftersun gel revealed that six N-nitrosamines were determined, three of which exceed the safety limit of 50 μg kg−1 defined by the European Regulation (i.e., NMEA 770 ± 90 μg kg−1, NPIP 50.6 ± 0.3 μg kg−1, and NPYR 114 ± 5 μg kg−1).*
>
> *Regarding the creams, only NMOR has been quantified in the first cream, which widely exceeds the safety limit, being found at a concentration of 870 ± 60 μg kg−1, while in the second cream only NMEA was quantified, which was also found to be above the safety limit, at a concentration of 560 ± 20 μg kg−1. Chromatograms of the sample solutions subjected to the proposed VA-DLLME method are shown in Fig. S2.†*
>
> *It should be noted that, as declared on the labels, these three samples analyzed included two ingredients that, even though they are permitted ingredients as they are a preservative (i.e., bronopol) and a pH regulator (i.e., triethanolamine), their reaction can unintentionally cause the formation of nitrosamines."*

Source: Schettino L, Benedé JL, Chisvert A. Determination of nine prohibited N-nitrosamines in cosmetic products by vortex-assisted dispersive liquid-liquid microextraction prior to gas chromatography-mass spectrometry. RSC Adv. 2023 Jan 19;13(5):2963-2971. doi: 10.1039/d2ra06553c.

This study should be added to the Safety Assessment to augment the discussion of Nitrosation. Specific recommendations for manufacturers on how to avoid the development of N-nitrosamines are clearly needed to avoid the public health failures demonstrated by the products tested for this study.

Thank you for your consideration of these comments.



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

Cosmetic Ingredient Review

Commitment & Credibility since 1976

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Thushara Diyabalanage, Ph.D., Scientific Analyst/ Writer, CIR
Date: May 30, 2025
Subject: Wave 2, Safety Assessment of Cocoyl Hydrolyzed Collagens

Please find the attached comments provided by the Personal Care Product Council on the Tentative Amended Report on Cocoyl Hydrolyzed Collagen Ingrdients. The comments are primarily editorial in nature and will be addressed following the June 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: May 27, 2025

SUBJECT: Draft Tentative Amended Report: Amended Safety Assessment of Cocoyl Hydrolyzed Collagen Ingredients as Used in Cosmetics (draft prepared for the June 9-10, 2025 meeting)

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

Key Issue

For safety studies from reference 5, it should be made clear that the Potassium Cocoyl Hydrolyzed Collagen tested was the material described (number average molecular weight about 600 and 30% solution in water). For example, Table 4 indicates that the Potassium Cocoyl Hydrolyzed Collagen was tested neat and undiluted, although this is correct, the solution tested undiluted was the 30% aqueous solution, so it would be better to list the vehicle as water and the concentration as 30%.

Additional Considerations

Introduction – Please add "Cocoyl" to "Sodium Hydrolyzed Collagen"

Chemical Properties – Please add that molecular weight reported was the number average molecular weight (to make it clear that it is not the weight average molecular weight).

Cosmetic Use – It would also be helpful to note that PCPC completed a concentration of use survey for Potassium Cocoyl Hydrolyzed Collagen and TEA-Cocoyl Hydrolyzed Collagen in 2022, but no uses were reported.

In the description of the EU restrictions, it should be made clear that the restrictions concern triethanolamine, not the Cocoyl Hydrolyzed Collagen moiety.

Dermal Irritation and Sensitization – Please correct: "rection" to "reaction"

It should be noted that a 10% dilution of the 30% active solution was tested in the Buehler guinea pig sensitization study. Please include the number of guinea pigs tested.

Please state the number of subjects tested with "undiluted" Potassium Cocoyl Hydrolyzed Collagen (which was tested as sold, a 30% aqueous solution).

Case Reports – It is not clear what is meant by "these allergens". Are these allergens the 4 samples of commercial hydrolyzed proteins?

Summary – Please add "the Panel" to "Subsequently, [the Panel] considered a re-review of these ingredients in 2002"

Since the Expert Panel requested UV absorption data, it would be helpful if it was mentioned in the Summary.

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Ferguson, M.S., Senior Scientific Analyst/Writer, CIR
Date: May 30, 2025
Subject: Wave 2 - Safety Assessment of Oxyquinoline and Oxyquinoline Sulfate as Used in Cosmetics

Please find attached the comments provided by the Personal Care Products Council (Council) on the Draft Amended Report on Oxyquinoline and Oxyquinoline Sulfate. The comments are editorial in nature and will be addressed following the June Panel meeting. Also received from the Council was a published study including the UV spectra of Oxyquinoline in 3 different solvents.[1] The absorption maximums (λ_{max}) of Oxyquinoline in chloroform, dimethyl sulfoxide, and methanol were determined to be 244, 319, and 241 nm, respectively.

References

1. Cipurkovi A, Horozi E, Mari A, Meki L, Junuzovi H. Metal complexes with 8-hydroxyquinoline: synthesis and in vitro antimicrobial activity. *Open Journal of Applied Sciences*. 2021;11(1):1–10.

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: May 27, 2025

SUBJECT: Draft Amended Report: Amended Safety Assessment of Oxyquinoline and Oxyquinoline Sulfate as Used in Cosmetics (draft prepared for the June 9-10, 2025 meeting)

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

Composition and Impurities – Oxyquinoline Sulfate was in the 19th USP with a purity of not less than 97%, not more than 101% calculated on an anhydrous basis. The current USP should be checked to see if it is still included.

Cosmetic Use – Please state the FDA product category for which the 0.15% concentration was reported (other hair preparations).

In the description of the EU cosmetic regulations, it should be noted that Oxyquinoline and Oxyquinoline Sulfate are also in Annex II (395) with the exceptions of the uses listed in Annex III.

Non-Cosmetic Use – As stated in comments when this re-review was opened, 21CFR310 is for ingredients that are **not** considered safe and effective. CFR310.545 is for a list of actives with "inadequate data to establish general recognition of the safety and effectiveness of the use of these ingredients for the specific uses listed. CFR310.531 says: "Based on evidence currently available, any OTC drug product offered for the treatment of boils cannot be considered generally recognized as safe and effective." It is also not correct that these ingredients are permitted in OTC oral health care products and as skin protectants (reference 12 is outdated and the link no longer works). The current website for FDA OTC drug monographs is at https://dps.fda.gov/omuf/monographsearch and the skin protectant monograph is at https://dps-admin.fda.gov/omuf/sites/omuf/files/primary-documents/2022-09/Final%20Administrative%20Order%20OTC000005_M016-

Skin%20Protectant%20Drug%20Products%20for%20OTC%20Human%20Use.pdf;
Oxyquinoline Sulfate is not listed in this current monograph.

It would be helpful to include the name (Quinoliol Sulfate) under which Oxyquinoline is listed as an active pesticide ingredient.

Developmental and Reproductive Toxicity; Summary; Table 4 – Please check the units for the 2-generation study in rats. The text and Table uses the same values for both mg/kg bw/day doses and ppm dietary concentrations. It is likely that the ppm dietary concentrations are correct (ppm concentrations in the diet do not result in the same values for mg/kg/day doses).

Baby rabbits should not be called “pups”. Please call them “offspring” or “kits”.

Cosmetic Ingredient Review

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To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Thushara Diyabalanage, Ph.D., Scientific Analyst/ Writer, CIR
Date: May 30, 2025
Subject: Wave 2 - Safety Assessment of *Paeonia suffruticosa*-Derived Ingredients

Please find attached comments of the Personal Care Products Council on the Draft Final Report of the Safety Assessment of *Paeonia suffruticosa*-Derived Ingredients (*PCPCcomments_Wave2_PaeoniaSuffruticosa_062025*). The comments are primarily editorial in nature and will be addressed following the June Panel meeting.

Also, please find the attached comment (*AnonymousComment_Wave2_PaeoniaSuffruticosa_062025*) provided by industry in response to the Tentative Report issued in December 2024. The comment provides further clarification on the definition of moutan bark, as well as what part of the plant is used by this supplier in manufacturing Paeonia Suffruticosa Root Extract. According to this information, Paeonia Suffruticosa Root Extract and Paeonia Suffruticosa Root Bark Extract may be the same ingredient, at least for this supplier. Therefore, please consider whether this information has resolved some of the uncertainty the Panel had as to whether the Paeonia Suffruticosa Root Extract contained the phytochemicals from the root bark as well. Please note that the actual data referred to in this comment have already been added to the report.

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: May 27, 2025

SUBJECT: Draft Final Report: Safety Assessment of *Paeonia suffruticosa*-Derived Ingredients as Used in Cosmetics (draft prepared for the June 9-10, 2025 meeting)

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

Key Issue
If pdf files of the Chinese language studies are available, please consider completing AI translations of these papers to obtain additional details.

Additional Considerations
Composition and Impurities – It is not clear why the information on *Paeonia suffruticosa* flower essential oil (reference 5) is being presented under Paeonia Suffruticosa Extract (defined as an extract of the whole plant).

Carcinogenicity, In Vitro Cell Transformation – It is not clear that Carcinogenicity, and In Vitro Cell Transformation are the correct heading and subheading for the studies included in this section. The studies all appear to be about reducing the potential for carcinogenicity, rather than the potential to cause cancer.

Please correct: "The lethal concentration (LC_{50}) values of human gastric cancer cells…." (please replace "of" with "for" or "in") as the LC_{50} is the concentration of a *Paeonia suffruticosa* root bark extract not the concentration of cells.

Anti-Photoaging; Summary – Please include the doses/concentrations of the root bark extract (also called root extract by the authors; reference 39) in the CIR report.

Irritation, In Vitro, Paeonia Suffruticosa Bark Extract – Although reference 31 says 100 ml was applied in the OECD TG 439 study, it was done in 6 well plates which, depending on the plate,

may have a maximum volume of about 16 ml. It probably should be 100 µl. Which is consistent with volumes of other components that are stated.

Table 2 – Based on the titles of the references associated with Table 2, only reference 5 may have looked at the composition of multiple plant parts. Reference 16 concerned the flower essential oil and based on the titles, references 20 and 21 were about cortex moutan and root bark (likely the same thing), respectively. It would be helpful to include the reference with the plant parts that were analyzed.

Did reference 16 include an analysis of the flowers? If only the essential oil was analyzed, either the flower column should be deleted, or the column heading should be changed to "flower essential oil".

The meaning of the blank cells in Table 2 is still not clear. The footnote to Table 2 says "Blank cells indicate specific compounds were not detected" (which suggests that each plant part was analyzed for all compounds listed). The response to PCPC comments says: "A blank cell means that a particular compound was not reported from that plant part in these investigations" (not reported could just mean they did not look for a component in the listed plant part – which is probably the more likely scenario based on the titles of the references).

Response to the insufficient data requirement for Paeonia suffruticosa-Derived Ingredients

CIR Executive Director,
Dr. Bart Heldreth

I am writing to submit our comments for the below two ingredients, which Tentative Report for Public Comment was released December 13, 2024.

- Paeonia Suffruticosa Root Bark Extract
- Paeonia Suffruticosa Root Extract

1. The root bark of Paeonia suffruticosa is extensively used in traditional Chinese medicine and is generally referred to as Moutan Bark（ボタンピ）in Japanese. In the Japanese Standards of Quasi-Drug Ingredients 2021, authorized by MJLW (Ministry of Health, Labour and Welfare Japan), Paeonia Extract is listed and defined as an extract obtained by extracting the root bark of the Paeonia suffruticosa Andrews (Paeonia moutan Sims) (Paeoniaceae) using ethanol[1)]. According to an open database site, Cosmetic-Info.jp, there are 13 raw materials used in cosmetics with the INCI name of Paeonia Suffruticosa Root Extract in Japan (https://www.cosmetic-info.jp/mate/result.php?jclnID=1638). 10 of them have been approved for quasi-drug use (i.e. meet the criteria for quasi-drugs), which means they are actually extracted from root bark (https://www.cosmetic-info.jp/mate/result.php?jsqiID=1720). Others may also be considered to be extracted from root bark because ボタンピ is either used in their Japanese Trade Name or in their product information. The reason why the INCI name was registered as Paeonia Suffruticosa Root Extract is because Paeonia Suffruticosa Root Bark Extract is not named in the PCPC's Dictionary.
   I apologize that the above web sites are in Japanese. If you click each single trade name of the raw materials, you may reach to the manufacturer website, but unfortunately most of them are in Japanese.
   In our opinion, there is a high possibility that the INCI name of Paeonia Suffruticosa Root Extract registered in US FDA are actually root bark extract, thus the existing data for Paeonia Suffruticosa Root Extract such as dermal irritation and sensitization data might be actually that of Paeonia Suffruticosa Root Bark Extract.

2. For Paeonia Suffruticosa Root Bark Extract, data on systemic toxicity endpoints is required. However, a NOAEL of 3000mg/kg/d using herbal mixture (containing 14.29% moutan cortex) has already been showed in the Tentative Report. If the reason that more data required is because that the test material is herbal mixture but not root bark itself?
   In addition, please refer to the attached document that showed single and repeated administration studies for moutan bark[2) 3)]. In the repeated administration study, after a treatment given orally for 21d with a daily doses of 1.5g/kg and 3g/kg, although a weak effects on hemolytic and lever function was found, since the effects were minimal, the authors concluded that there is no significant toxicological issues for moutan bark.

3. For the INCI Paeonia Suffruticosa Root Extract, I would like to submit our Maximum concentrations of use for products registered in the US as below. As I mentioned in 1, the INCI name was registered as Paeonia Suffruticosa Root Extract but the raw material is actually extracted from Root bark.
   Maximum concentrations of use: 0.002%
   Product Category:
   (14) Skin care preparations, (creams, lotions, powder, and sprays). (f) Moisturizing.

Attached documents

1) The Japanese Standards of Quasi-Drug Ingredients 2021.pdf
   Note: This is only in Japanese. Please search the word “Paeonia Extract” (may take a little while), and refer to the corresponding part highlighted yellow.
2) Toxicological Studies on Biological Effects of Herbal Drug Extracts_Japanese .pdf
   Note: This is an original paper in Japanese but with an English abstract. Please refer to the corresponding part highlighted yellow in P.683.
3) Toxicological Studies on Biological Effects of Herbal Drug Extracts_English.docx
   Note: This an English Translation ver. for your reference. Please refer to the corresponding part highlighted yellow in P.17.

Taken together, we would like to ask for your further consideration for the safety assessment of the two ingredients.

Sincerely yours

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Ferguson, M.S., Senior Scientific Analyst/Writer, CIR
Date: May 30, 2025
Subject: Wave 2 - Safety Assessment of Propylene Carbonate as Used in Cosmetics

Please find attached the comments provided by the Personal Care Products Council on the Draft Final Amended Report on Propylene Carbonate. The comments are primarily editorial in nature and will be addressed following the June Panel meeting; however, a question was posed regarding the inhalation boilerplate language in this report. The Panel should review this comment and address it accordingly.

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: May 27, 2025

SUBJECT: Draft Final Amended Report: Amended Safety Assessment of Propylene Carbonate as Used in Cosmetics (draft prepared for the June 9-10, 2025 meeting)

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

Key Issue
Discussion – Is the inhalation boilerplate language appropriate for Propylene Carbonate which has a basically negative 90-day (OECD 413) rat inhalation study?

Additional Considerations
Repeated-Dose Toxicity; Summary – Since the 90-day rat inhalation study was basically negative (local NOAEC of 100 mg/m^3), and the text does not include any details of the endpoints examined, it would be very helpful to state that it was an OECD TG 413 study in the text, so the reader does not have to check the Table to determine it was a comprehensive study.

Summary – In the Summary, it would be helpful to state that Propylene Carbonate was degraded to propylene glycol.

Please note that the “maximization assay” was in humans.

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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: May 30, 2025
Subject: Wave 2 - Safety Assessment of Pyrogallol as Used in Cosmetics

Please find attached the comments provided by the Personal Care Products Council on the Draft Amended Tentative Report on Pyrogallol. The comments are primarily editorial in nature and will be addressed following the June 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: May 27, 2025

SUBJECT: Draft Tentative Amended Report: Amended Safety Assessment of Pyrogallol as Used in Cosmetics (draft prepared for the June 9-10, 2025 meeting)

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

Memo; Cosmetic Use; Summary – The report of Pyrogallol as an incidental ingredient from use of some plant extracts was from cosmetic product manufacturers rather than ingredient suppliers.

Short-Term, Oral, old report summary – It is not clear what is meant by 150% mortality. Should this be 50 or 100%?

Genotoxicity – Please correct: “Ames tested when tested in 3 hair gel formulations” (delete “ed” in the first “tested”.

Carcinogenicity, Dermal – In the paragraph describing the results of the mouse NTP bioassay, please correct “lesions at the site of application occurred to be more severe in female mice” (either change “occurred” to “appeared” or change “occurred to be” to “were”)

Summary – Please correct: “rang-finding study” (add “e”)

Please correct: “included with 5%” (change “included” to “induced”)

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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: May 30, 2025
Subject: Wave 2 - Safety Assessment of Tetrabromophenol Blue as Used in Cosmetics

Please find attached the comments provided by the Personal Care Products Council on the Draft Final Report on Tetrabromophenol Blue. The comments are primarily editorial in nature and will be addressed following the June 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: May 27, 2025

SUBJECT: Draft Final Report: Safety Assessment of Tetrabromophenol Blue as Used in Cosmetics (draft prepared for the June 9-10, 2025 meeting)

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

Key Issue
Discussion – As a general method of manufacture method from The Merck Index has been added to the report, the following statement in the Discussion needs to be revised: "The Panel also noted a lack of method of manufacturing".

Additional Considerations
ADME, Oral, Parenteral – The oral and parenteral sections start with the following sentences that suggests that the same animals used in the dermal study were used in the oral and parenteral studies. Oral: "The same animal study groups of the dermal study described above…." Parenteral: "The same animal study groups of the dermal and oral studies described above…." Since it is unlikely that the same animals were used, it would be clearer to state: Oral: "Groups of the same strain of rat used in the dermal study described above …." Parenteral: "Groups of the same strain of rat used in the dermal and oral studies described above …

Subchronic, Oral (second paragraph); Summary – Please indicate whether the changes in platelet values and erythrocyte counts were increases or decreases.

Ocular Irritation – Unless more than one sample of Tetrabromophenol Blue was tested in the eye irritation study, "test items" should be revised to "test item" (or Tetrabromophenol Blue).

Summary – In the Summary, it would be useful to include the half-life values determined in the oral and iv toxicokinetic studies.