Data Supplement

4-Amino-*m*-Cresol

BHA

t-Butyl Alcohol

Lanolin

MIBK

Toluene

EXPERT PANEL MEETING
September 30 – October 1, 2024

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: September 20, 2024
Subject: Wave 2 - Amended Safety Assessment of 4-Amino-*m*-Cresol as Used in Cosmetics

Please find attached the comments provided by the Personal Care Products Council on the Draft Final Amended Report on 4-Amino-*m*-Cresol. The Panel will need to address the comment regarding the wording of the Discussion. The Panel should review the transcripts of the prior meeting, data from the report, and the Discussion to determine if revisions are necessary. The Council correctly noted that there is a positive LLNA study for 4-Amino-*m*-Cresol. 4-Amino-*m*-Cresol was not irritating or sensitizing in a guinea pig maximization test with induction at 3% and challenge at 1, 2, and 3%; and irritation was not observed in two in vitro studies with human epidermal keratinocytes and in a guinea pig irritation study at 3%.

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: September 18, 2024

SUBJECT: Draft Final Report: Amended Safety Assessment of 4-Amino-m-Cresol as Used in Cosmetics (draft prepared for the Sept 30-Oct 1, 2024 CIR meeting)

The Personal Care Products Council respectfully submits the following comments on the draft final report, Amended Safety Assessment of 4-Amino-m-Cresol as Used in Cosmetics.

Key Issue

Discussion – The third paragraph of the Discussion suggests that lack of effects in other toxicity endpoints are being used to address the mixed genotoxicity results and lack of carcinogenicity data. The concern for potential carcinogenicity of 4-Amino-m-Cresol is mitigated by the low dermal absorption and the intermittent use of products containing this ingredient. The lack of histopathological changes in the 13-week study also supports a lack of toxicity. But does the Expert Panel want to imply that the negative developmental toxicity studies and the dermal irritation and sensitization studies add to the weight of evidence to mitigate concerns regarding carcinogenicity? Since there was a positive LLNA, it is not appropriate to state that the results of dermal sensitization studies were negative.

Additional Considerations

Chemical Properties – Please delete "Tables" and remove the paragraph break before "Table 1".

Method of Manufacture – The CIR report on Coal Tar is not an appropriate reference for "non-amino-substituted cresols are traditionally obtained via distillation of coal tar". The FDA hair dye page https://www.fda.gov/cosmetics/cosmetic-products/hair-dyes#coal provides a better explanation for the history of the term coal tar hair dye and explains that petroleum is the source for most hair dyes now.

Developmental and Reproductive Toxicity, old report summary – Please correct "were dose[d] orally" (add "d").

Summary – Please correct: “in a L5178Y mouse lymphoma assays” (either delete “a” or delete “s” in assays)

Please correct: “The Panel performed an MOE calculation was performed” – performed does not need to be stated twice.

References – References 4 and 6 are the same SCCP 2005 opinion on 4-Amino-m-Cresol.

Cosmetic Ingredient Review

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Monice Fiume, M.B.A., Senior Director, CIR
Date: September 20, 2024
Subject: Wave 2 - Amended Safety Assessment of BHA as Used in Cosmetics

Enclosed are comments from the Personal Care Products Council on the Draft Final Amended Report of the Safety Assessment of BHA as Used in Cosmetics for your review. These are identified as *PCPCcomments_BHA_Wave2_092024*. The majority of the comments appear to be editorial in nature.

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: September 19, 2024

SUBJECT: Draft Final Report: Amended Safety Assessment of BHA as Used in Cosmetics (draft prepared for the Sept 30-Oct 1, 2024 CIR meeting)

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

Abbreviations; Table 4 – Despite the response to comments indicating that this was corrected, the following error is still present in the meeting draft. "Consumer, Toiletry and Fragrance Association" needs to be corrected to "Cosmetic, Toiletry and Fragrance Association" both in the list of abbreviations and in a footnote to Table 4.

Chemical Properties, old report summary – Please correct: "using the equivalent quality of either antioxidant alone" (it would make more sense if "quality" was "quantity").

Non-Cosmetic Use – BHA itself is not a "pressure-sensitive adhesive" it is approved for use in pressure-sensitive adhesives.

Short-Term, last paragraph old report summary – What concentrations of BHA were in the diet of rats in which proliferative effects in the forestomach were observed?

Developmental and Reproductive Toxicity – Were any effects observed at 10 mg/kg (reference 17)?

Carcinogenicity, Oral, old report study – Please revise "either 0, 1.35, or 67.5 mg/kg in the diet" to "either 0, 1.35, or 67.5 mg/kg of diet" to make it clear that in this case, kg represents the diet not body weight (the sentences also starts with "Rats were given diets containing BHA" – so it is clear the rats were dosed in the diet).

Carcinogenicity; Summary – For safe harbor values, California's Office of Environmental Health Hazard Assessment (OEHHA) uses "maximum allowable dose" (MADL) for reproductive and

developmental toxicants. They use "no significant risk level" (NSRL) for carcinogens. Since BHA is listed as a carcinogen on Proposition 65 the 4000 µg/day value needs to be listed as a NSRL rather than a MADL in both the Carcinogenicity and Summary sections.

Anti-Carcinogenicity – Please add the doses of BHA used in reference 21.

Immunomodulatory – Please state the frequency of treatment, e.g., daily, used in the mouse study described in reference 30.

Effects on Blood-Brain Barrier – This heading should be revised as the study looked at enzyme activity in the brain and did not assess effects on the blood-brain barrier.

Case Reports, old report summary – Please identify "the chemical".

Summary – Please delete "disruptive" in "potential endocrine disruptive effect"

Summary – As the exposure estimate for other manicuring products has been removed from Table 4, it should be removed from the Summary and replaced with 0.2 mg/day BHA from use of a face and neck product to be consistent with the rest of the report.

Discussion – It is not clear what is meant by "non-physiological concentrations" as BHA does not have a "physiological" role.

Table 4 – It would be helpful to note that SCCS and Api et al. (2008) use 90^{th} percentile values for product exposure and that the product exposure values from these sources already include retention factors.

Cosmetic Ingredient Review

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Monice Fiume, M.B.A., Senior Director, CIR
Date: September 20, 2024
Subject: Wave 2 - Amended Safety Assessment of *t*-Butyl Alcohol as Used in Cosmetics

Enclosed are comments from the Personal Care Products Council on the Draft Final Amended Report of the Safety Assessment of *t*-Butyl Alcohol as Used in Cosmetics. These are identified as *PCPCcomments_t-ButylAlcohol_Wave2_092024*. The majority of the comments are editorial; however, some suggestions for calculating daily exposure were 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: September 18, 2024

SUBJECT: Draft Final Report: Amended Safety Assessment of t-Butyl Alcohol as Used in Cosmetics (draft prepared for the Sept 30-Oct 1, 2024 CIR meeting)

The Personal Care Products Council respectfully submits the following comments on the draft final report, Amended Safety Assessment of t-Butyl Alcohol as Used in Cosmetics.

Abbreviations; Occupational Exposure – Please correct: "National Institute of Occupational Safety and Health" to "National Institute for Occupational Safety and Health"

Introduction – Please state the species (mice) used in the liquid diet study.

Cosmetic Use – It would be helpful to include use information from the 2023 RIFM assessment (reference 6).

Phototoxicity – Please delete the subheading "Human" as measuring UV absorption spectra is not a study done in humans. The CIR report format outline https://www.cir-safety.org/sites/default/files/CIR%20Report%20Format%20Outline.pdf includes UV absorption in the Chemistry section of CIR reports.

Summary – Please correct: "maximum use concentration of use for t-Butyl Alcohol" (delete first "use")

Please correct: "The major urinary metabolites of t-Butyl Alcohol……., in rat urine." (in rat urine should be deleted)

It is not clear if the sloughing occurred in the testes of treated or control rats.

Please correct: "nervous toxicity observed" (add "system")

If the MoE calculations are not changed, the Summary should state how the NOAEL of 160

mg/kg was “adjusted”, e.g., adjusted for a short duration of exposure.

Table 5 – Rather than citing secondary references for the use information, it would be helpful if primary references were cited. If primary references are not included, the table should note that the use information from SCCS and Api et al. (2008) already includes retention factors and that they are 90th percentile values. The range of retention factors should be described.

Shaving cream may not be not an appropriate surrogate for beard softener. One product manufacturer suggests using an amount the size of a nickel or dime for a “beard conditioner”. If use information is not available for a product category, no exposure estimate should be completed. Product categories for which product exposure information could still be included in this table with the Daily Exposure column filled in with something like “daily exposure information for this product category was not available”.

An asterisk is missing from the first footnote (or another footnote needs to be added to define what “*” means.

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: September 20, 2024
Subject: Wave 2 - Amended Safety Assessment of Lanolin and Lanolin-Derived Ingredients as Used in Cosmetics

Please find attached the comments provided by the Personal Care Products Council on the Draft Final Amended Report on Lanolin and Lanolin-Derived ingredients.

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: September 18, 2024

SUBJECT: Draft Final Report: Amended Safety Assessment of Lanolin and Lanolin-Derived Ingredients as Used in Cosmetics (draft prepared for the Sept 30-Oct 1, 2024 CIR meeting)

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

Key Issue

Discussion – As noted in the CIR report, Lanolin is used in OTC drug products intended for damaged skin. The Discussion should not state: "The Panel cautioned that Lanolin should not be used on damaged skin, especially in high-risk populations for sensitivity (e.g., pediatric and geriatric populations)." Please delete this sentence.

Discussion – As nothing is "risk-free", please delete the following sentence: "Suppliers and users of these ingredients must accept responsibility for assuring that these ingredients are risk-free." This sentence could be taken out of context and be thought to refer to endpoints other than infectious agents.

Additional Considerations

Introduction – Rather than stating that "lanolinamide DEA is safe with several qualifications", it would be helpful to note that the conclusion is safe when formulated to be non-irritating with additional qualifications based on the presence of an amide group.

Clinical Studies, old report summary – In the paragraph that states: "the incidence of hypersensitivity to all topical medicaments was 14%" it also states: "The difference between these total values of 12% and the overall total of 14% was not stated." It is not clear what 12% represents.

Clinical Reports – In the study of 430 patients, it would be helpful if the results for Lanolin were also stated.

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Thushara Diyabalanage Ph.D., Senior Scientific Analyst/Writer, CIR
Date: September 20, 2024
Subject: Wave 2 - Amended Safety Assessment of MIBK as Used in Cosmetics, Council Comments

Enclosed are the comments from Personal Care Products Council (PCPC) on the Draft Final Amended Report of the Safety Assessment of MIBK as used in Cosmetics.

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: September 18, 2024

SUBJECT: Draft Final Report: Amended Safety Assessment of MIBK as Used in Cosmetics (draft prepared for the Sept 30-Oct 1, 2024 CIR meeting)

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

Abbreviations – For ID_{50}, either "median" should be added to the definition, or 50 should be removed from the abbreviation.

ADME, old report summary – Although the summary reflects what was said in the original CIR report. it does not accurately reflect the original study (Dowty, B. J., J. L. Laseter, and J. Storer. 1976. Transplacental migration and accumulation in blood of volatile organic constituents. Pediatric Res. 10:696–701 https://www.nature.com/articles/pr1976117#preview). The investigators measured various solvents in matched maternal and cord blood. Quantitative values for MIBK are not provided. The statement that "MIBK has the potential to enter the umbilical cord and cross the placenta" suggests that MIBK is moving from the fetus/infant to the mother. As the paper did not provide any information on directionality, it would be appropriate to delete "enter the umbilical cord" and just say that "MIBK has the potential to cross the placenta".

Discussion – In the second paragraph, please correct: "no concentrations of use of MIBK have were reported" (delete "have").

Cosmetic Ingredient Review

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, M.S., Senior Scientific Analyst/Writer, CIR
Date: September 20, 2024
Subject: Wave 2 - Amended Safety Assessment of Toluene as Used in Cosmetics

Enclosed are comments from Personal Care Products Council on the Final Report on the Amended Safety Assessment of Toluene as used in Cosmetics.

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: September 18, 2024

SUBJECT: Draft Final Report: Amended Safety Assessment of Toluene as Used in Cosmetics (draft prepared for the Sept 30-Oct 1, 2024 CIR meeting)

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

Cosmetic Use – In the airbrush paragraph, please correct "these ingredients" to "Toluene" or "this ingredient"

Cosmetic Use – A better reference for the frequency of use for nail products (and other information e.g., nail surface area, concerning nail cosmetic use) is the following paper: Ficheux AS, Morisset T, Chevillotte G, et al. 2014. Probabilistic assessment of exposure to nail cosmetics in French consumers. Food and Chemical Toxicology 66:36–43.

ADME, old report summary – Please add a reference for the third paragraph of the old report summary.

Reproductive and Developmental Toxicity – Although it may be stated in the table, the text should provide more details about the exposure used in reference 34 (it currently says "pre-natal and post-natal exposure). If this is an OECD Guideline study, identifying the guideline would also be sufficient.

Carcinogenicity, old report summary – The results of the 13-week study should not be presented in the Carcinogenicity section.

Hepatotoxicity – Were the controls used in reference 87 really given "physiological serum"? Perhaps this should be "physiological saline".

Occupational/Epidemiology/Case Reports, old report summary – Toluene concentrations in blood (second paragraph) are given in two different units, µmol/l and mg/l. It does not make

sense to say that Toluene levels "ranged from 20 µmol/l to approximately 0.94 mg/l". Either transform one value to the other units, or do not say there was a "range" of concentrations.

MoE/MoS Calculations – What concentrations of Toluene were in the nail products for which the DTSC estimated exposure was 7760 µg/day?

MoS Calculation based on the EPA RfC – This calculation should not be called an Oral RfD as that implies it is an EPA value. The calculation is the dose estimated for exposure to the RfC for 24 hours assuming 100% absorption. It is conservative as the ADME section states that 50% of Toluene is absorbed following inhalation exposure.

In the calculation it says "60 kg (rat bw)" "rat" needs to be corrected to "human"

MOE calculation based on NOAEL for DART – Rather than "$Oral_{NOAEL}$", it should be made clear that it is a dose calculated from inhalation exposure assuming 100% absorption.

Since the primary exposure to Toluene is through the nails and/or inhalation exposure, it is not clear why the goal is to estimate oral exposure.

Epidemiological Studies - Please state the confidence intervals for the odds ratios (reference 123). Currently the odds ratios are stated, and it states "95% CI" but the values for the 95% confidence intervals are not stated. It is helpful to know if the 95% confidence intervals include 1.

Summary – For the inhalation exposure studies, please include the hours/day, days/week the animals were exposed (one example where it is missing is for the 14-day study in rabbits exposed to 1000 mg/l).

When describing the MoE calculations, it should state that estimated exposure was based on nail products containing 20% Toluene.

Discussion – In the second paragraph, "MOS" should be "MOE" (or "MOE/MOS").