

Data Supplement

4-Amino-*m*-Cresol

BHA

Copper Gluconate

Lanolin

MIBK

Pentapeptides

Phthalates SM

t-Butyl Alcohol

Toluene

Read-Across Working Group

EXPERT PANEL MEETING

March 28-29, 2024



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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 18, 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 Amended Report on 4-Amino-*m*-Cresol.



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 18, 2024

SUBJECT: Draft Report: Amended Safety Assessment of 4-Amino-m-Cresol as Used in Cosmetics (draft prepared for the March 2024 meeting)

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

Key Issue

The description of the margin of safety calculation for use at 0.14% states: “In consideration of the absence of dermal absorption data for 4-Amino-m-Cresol at the maximum use concentration of 0.14%” as justification for use of a 50% default dermal penetration value. It is not correct that there are no data at concentrations relevant to the 0.14% maximum use concentration. There is an *in vitro* dermal penetration study cited to the ECHA dossier (reference 5) that tested dermal penetration at 0.1%, 0.5%, 1.5% or 2%, which includes concentrations that bracket the maximum use concentration. The results at 0.5% were 0.068%, indicating that the 50% assumption vastly overestimates dermal penetration. If the Expert Panel wants to include the calculation assuming 50% absorption, the reason should be they wanted to consider a very conservative assumption, not that dermal penetration data at relevant concentrations were lacking. The reason for using the 50% dermal absorption assumption also needs to be corrected in the Summary.

Additional Considerations

Chemistry – Since the hemisulfate was tested in some of the studies, it would be helpful if information on it was also presented in the Chemistry section.

Definition and Structure – Please correct (add “conforms”): “is the substituted aromatic compound that [conforms] to the structure”

Dermal Absorption, In Vitro – In the dermal penetration study in pig skin (cited to reference 5), a radiolabeled compound was used. Therefore, if they only were measuring radioactivity it should say “radioactivity” rather than “test material”.

ADME, Animal, Dermal – In the first sentence of the results of the dermal penetration study in rats, it would be helpful to state what the percentage values represent (likely percent of the applied dose as stated later in the paragraph).

ADME. Animal, Dermal – Please correct: “withing” (delete “g”) (occurs 3 times in this section)

Short-Term, old report summary – The route of exposure was oral. Therefore, “route of administration not specified” needs to be corrected to “method of oral administration not specified”.



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc., Senior Scientific Analyst/Writer, CIR
Date: March 18, 2024
Subject: Amended Safety Assessment of BHA as Used in Cosmetics

Please find attached comments received from the Personal Care Products Council on the Amended Safety Assessment of BHA as Used in Cosmetics.



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 18, 2024

SUBJECT: Draft Report: Amended Safety Assessment of BHA as Used in Cosmetics (draft prepared for the March 2024 meeting)

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

Introduction – In the first sentence the second “as used in cosmetic formulations” needs to be deleted.

Dermal Absorption, In Vitro; reference 12 – If available, more details of this dermal penetration study (reference 12) should be presented in the CIR report as it was not summarized in the original re-review. What vehicle was used? What was the receptor fluid? It is not clear what is meant by “continuous application”. The reference section indicates that this study was submitted “for review at the September 8-9, 2023, meeting. If this date is correct, this study was not considered during the original review and the text should not be italicized.

ADME, In Vitro – Please identify what was found at a concentration of 26 µg/ml. Was this the total concentration in blood, or the concentration bound to albumin?

Short-Term, Oral; Summary – Although the ECHA dossier did not give additional details about the 6-week study in rats with a LOEL of 63,000 mg/kg, it did state that the information was from the RTECS database (the following reference is provided: AJEBAK Australian Journal of Experimental Biology and Medical Science. (Adelaide, S.A., Australia) V.1-64, 1924-86. Volume(issue)/page/year: 39,353,1961). Without additional information, this study should be deleted from the CIR report.

Subchronic, Oral – Although the ECHA dossier did not give additional details about the 16-week study in rats with a LOEL of 9900 mg/kg/day, it did state that the information was from the RTECS database (the following reference is provided: TRENAF Kenkyu Nenpo-Tokyo-toritsu Eisei Kenkyusho. Annual Report of Tokyo Metropolitan Research Laboratory of Public Health.

V.1- 1949/50- Volume(issue)/page/year: 22,231,1970). Without additional information this study should be deleted from the CIR report.

DART, Oral, old report summary – Since only rats were tested, please delete “of either species” in the following: “no significant embryotoxic or teratogenic effects were seen in any strain of either species (albino or hooded).”

The last sentence of the first paragraph is talking about 2 species, rats and guinea pigs. Rather than saying “in either animal” it should say “in either species”.

DART, Oral – In the description of reference 16, what dose(s) of BHA were associated with increased organ weights, decreased mating rate and longer time to mating?

Tumor Promotion, Other Routes, old report summary – What doses were used in the intraperitoneal study? If an initiator was used in this study, it should be identified.

Endocrine Effects – At what concentrations were the effects observed in reference 19?

Please check the units for the concentrations tested in references 21 and 23, as mM concentrations seem very high. In addition, the description of reference 21 also says the highest concentration tested was 300 μ M (if the units should be μ M, this also needs to be corrected in the Summary).

What concentrations of BHA resulted in anti-glucocorticoid-like and anti-androgen activity (reference 24)?

Immunomodulatory Effects – As it is likely that whole spleens were isolated and weighed, please delete “samples” in “spleen samples were isolated and weighed individually”.

Hormonal Effects, old report summary – The following sentence does not make sense. Perhaps one of the prostaglandin E₂ should be a different prostaglandin. “In vitro, 1.06 μ M BHA inhibited prostaglandin E₂ biosynthesis by 28% and stimulated prostaglandin E₂ biosynthesis by 34%.”

Effects on Human Astrocytes – How long were the NHA-SV40LT cells treated with BHA?

Irritation, Animal, old report summary – If “0.005 x 0.1%” is the correct calculation, the “actual BHA concentration” should be 0.0005% not 0.005% as stated in the CIR report.

Irritation, Human, old report summary – What was the concentration of BHA in the 3 cosmetic pastes tested in 10 subjects?

Case Reports, old report summary - Please revise the following: “Patch tests with the mayonnaise were positive for 2% BHA in the patient and negative in 3 controls”. Perhaps it should say: “Patch test with the mayonnaise and 2% BHA were positive in the patient and negative in 3 controls.”

Exposure calculations; Table 4; Reference 30 – Please use the most recent SCCS Notes of Guidance (12th revision 2023).

Table 4 should note that the Daily Exposure by Product Category from the SCCS Notes of Guidance include the retention factors. If product use values are obtained from other sources, retention factors should be applied. For example, based on the Notes of Guidance, hair styling products have a retention factor of 0.1, which would result in the exposure from hair spray to be reduced to 500 mg/day compared to 5000 mg/day (the value in the table). The table should note the percentile level for the values from CTFA habits and practices studies.

Rather than mostly relying on the SCCS Notes of Guidance for product exposure, it would be helpful to use the following RIFM paper which more clearly identifies the sources of the values used (see Table 3 of this paper).

Api AM, Basketter DM, Cadby PA, et al. 2008. Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. Regul Tox and Pharm 52: 3-23.

Exposure amount for bath oil, salts, etc., products added directly into the bath, is not a good surrogate for the category, bath soaps and detergents which are products used directly on the skin and rinsed off. The shower gel exposure value would be a better surrogate for bath soaps and detergents.

Products defined as “other” means it does not fit into the existing FDA cosmetic product categories. Thus, either the product should be defined, and exposures referenced, or exposure cannot be estimated for these products. In the latter, the exposure would need to be within the exposures encompassed elsewhere in the table to be considered “safe as used”. In Table 4, exposure should not be estimated for the “other manicuring preparations” containing 0.15% BHA. Because we do not know how the other manicuring preparation is used, it is not possible to estimate the amount of product that would be used. Because there is a nail polish and enamel category and the respondent did not select that category, exposure values for nail polish and enamel should not be used.

Summary – Please indicate the direction of the effect on body weight gain by testosterone propionate alone and combined with BHA (it currently just says it was “affected”).



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc., Senior Scientific Analyst/Writer, CIR
Date: March 18, 2024
Subject: Safety Assessment of Copper Gluconate as Used in Cosmetics

Please find attached comments received from the Personal Care Products Council on the Draft Report of the Safety Assessment of Copper Gluconate as Used in Cosmetics.



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 18, 2024

SUBJECT: Draft Report: Safety Assessment of Copper Gluconate as Used in Cosmetics
(draft prepared for the March 2024 meeting)

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

Key Issue

The draft ATSDR profile on copper should be used as a source for references and should not be cited in the CIR report. The acute minimal risk level (MRL) has not been finalized by ATSDR and should not be mentioned in the CIR report. If the ATSDR profile on copper is finalized before the CIR report goes final, the MRL should be in the CIR report, but it should not be in the Non-Cosmetic use section. Any risk assessment value such as an MRL presented in a CIR report should include a description of the basis for the value. In this case the acute oral MRL was based on gastrointestinal effects in women who drank water containing copper sulfate.

Additional Considerations

Cosmetic Use – Please correct “Copper Gluconate in a leave-on formulation is up at 0.006% in eyeliners” (deleted “up at”)

Acute, Oral; Summary – There are two results presented for the 2400 mg/kg dose group (8/10 deaths and 5/10 deaths). It is likely that the second value is for the 1800 mg/kg dose group.

Short-Term and Chronic; Table 3 – In the monkey study it currently states: “levels of the antibodies Ki67 and MT1 were significantly greater in liver tissue of treated and young monkeys.” This suggests that Ki67 and MT1 are antibodies. Ki67 is a protein used as a marker for cell proliferation. MT1 is the protein metallothionein 1. It is likely that antibodies for these proteins were used to visualize Ki67 and MT1 to determine that the proteins were increased in the liver following treatment with Copper Gluconate.

Short-Term and Chronic – Did the QSAR model as described in the ECHA dossier identify the

target organ for the predicted LOAEL?

Tumor Promotion – As metallothionein induction was also likely observed at doses greater than 0.1% Copper Gluconate, it would be helpful if “ \geq ” was also added before 0.1% in the following: “Copper accumulation and metallothionein induction were apparent at dose of \geq 0.3% and \geq 0.1% Copper Gluconate, respectively.”

Exposure Assessment – If a value is not used in the exposure estimate calculations, it does not need to be presented. For example, the surface areas are not necessary, nor are the body weights if the values are not normalized to kg.

Exposure Assessment, baby shampoo – Is the value of 9.06 g/day really for baby shampoo or is this value for shampoo in general? Please revise “Estimated daily amount applied in baby shampoo” to make it clearer that this is the amount of shampoo applied (not the amount of Copper Gluconate), e.g., Estimated daily amount of baby shampoo applied.

Exposure Assessment, make-up remover – Please revise “Estimated daily amount applied in a make-up remover” to make it clearer that this is the amount of product applied (not the amount of Copper Gluconate), e.g., Estimated daily amount of make-up remover applied.

Summary – Please correct: “in a leave-on formulation is at up to 0.006% in eyeliners” (delete “at up to”)

Summary – It would be helpful to also note that copper levels in the liver were also increased in the 92-day mouse study.

Summary – The modeled dermal penetration study should be presented elsewhere in the report or it should be deleted from the Summary.

Table 3 – In the second experiment in mice treated with Copper Gluconate in drinking water, did they really limit the control group to the same amount of distilled water consumed by the treated group? (the Protocol column currently states: “Control groups consumed the same amount of distilled water” but the Dose/Concentration column states “amount of water not specified”). It is more likely that both groups got to drink water ad libitum and water intake was measured and no differences were found.



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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 18, 2024
Subject: Wave 2 - Amended Safety Assessment of Lanolin-Derived Ingredients as Used in Cosmetics

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



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 18, 2024

SUBJECT: Draft Report: Amended Safety Assessment of Lanolin-Derived Ingredients as Used in Cosmetics (draft prepared for the March 2024 meeting)

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

Introduction – The word “assessment” is missing from the following: “and it is those summary data that are reported in this safety”

Method of Manufacture, Hydroxylated Lanolin – “dial” should be “diol”

Composition and Impurities – It would be helpful to include some current specification, e.g., USP, Food Chemical Codex, in this section.

Composition and Impurities, Lanolin, old report summary – Please correct “arid” to “and”

Non-Cosmetic Use – The summary of 21CFR Part 310 concerning lack of data to support safe and effective use of Lanolin as drug ingredients is misleading. It should be made clear that this section concerns the use of Lanolin as an active for the specified uses. It could be in these products as an inactive ingredient.

The uses of Lanolin in FDA’s Inactive Ingredients Database <https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-approved-drug-products-search-frequently-asked-questions> should be summarized in the Non-Cosmetic Use section. These uses should also be mentioned in the Summary.

Subchronic – The purity of the Lanolin Acid (>90%) and Lanolin Alcohol (>90%) tested in the 90-day studies included in the ECHA dossier should be added to the CIR report.

The reference for the 90-day study of Lanolin Acid should be 10 not 11 as stated in the first paragraph.

Comedogenicity, old report summary – What were the concentrations of Lanolin ingredients in products that were comedogenic?

Comedogenicity, Hydroxylated Lanolin – Was cottonseed oil really a positive control? It was not comedogenic in this study. Did the authors have any explanation as to why their positive control was not positive?

Dermal Irritation and Sensitization, old report summary – In the paragraph that starts with “Numerous patch test were conducted on volunteers”, were the patch tests of humans single or repeated patch tests?

It should be noted that the ECHA dossier disregarded the Draize dermal irritation study of Lanolin Alcohol in rabbits. It was not considered sufficient for use in classifying Lanolin Alcohol.

Photosensitization/Phototoxicity – If there was information on the light exposure in the original report, it should also be presented in this report.

Clinical Studies, old report summary – Was the 14% incidence of hypersensitivity to topical medicaments for all topical medicaments? If it was just for products that contained Lanolin (or other Lanolin ingredients), that should be stated.

Clinical Studies; Summary – Please clarify why Lanolin was selected as Contact Allergen of the Year, e.g., to bring attention to the described characteristics of Lanolin sensitization potential.

Clinical Reports – What concentrations of the 10% Lanolin/mineral oil product were tested (reference 37)?

Reference 34 – Please correct: “infectiosn”



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Thushara Diyabalanage Ph.D.
Date: March 15, 2024
Subject: Wave 2 – PCPC comments on the draft Final Amended Report of the Safety Assessment of MIBK

The comments of the Personal Care Products Council (PCPC) on the draft Final Report on the Amended Safety Assessment of MIBK were received. They highlighted the need to revise the paragraph related to use of MIBK as a solvent denaturant to resolve a possible confusion and also the need to mention the mode of action for the kidney tumors in the Discussion as key issues, in addition to a few additional considerations.

These comments and the responses may be found herein as *PCPCcomments_MIBK_Wave2_032024* and response-*PCPCcomments_MIBK_Wave2_032024*.



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 13, 2024

SUBJECT: Draft Final Report: Amended Safety Assessment of MIBK as Used in Cosmetics
(draft prepared for the March 2024 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.

Key Issues

Discussion – The paragraph regarding use of MIBK as a denaturant is confusing. This paragraph should be revised to make it clear that 4% is the maximum concentration MIBK added to alcohol to denature it, so it is not orally consumed, rather than a maximum concentration in cosmetic products. It is not clear that “(that can be consumed)” is necessary. The purpose of a denaturant is to make alcohol unpalatable to drink. This should be clearly explained, or “that can be consumed” should be deleted as it suggests the denatured alcohol can be consumed.

The mode of action for the kidney tumors in rats should also be mentioned in the Discussion.

Additional Considerations

Acute, Oral, old report summary; Short-Term, Oral, old report summary – Rather than “average lethal dose” it should be “median lethal dose”.

Subchronic, Inhalation, old report summary – “127 mg/MIBK for 4 h/day” is likely missing “m³” after the first ”/”

Occupational Exposure – Please correct “National Institute of Occupational Safety and Health” (“of” needs to be corrected to “for”)

The description of reference 19 still seems to be incomplete as no results for MIBK in urine are stated and it does not note whether the authors considered urinary MIBK as a useful biomarker for MIBK exposure. Although the ACGIH limit for MIBK may have been 50 ppm when the study was completed, it is currently 20 ppm, so it is confusing to state it is 50 ppm in the

paragraph about this study when it is listed as 20 ppm earlier in this section.

Summary – The Summary states: “The TWA concentration of the urine of the workers...” this needs to be corrected as TWA generally refers to air concentrations.

Conclusion – In the footnote to the conclusion, it would be helpful to note that the use concentrations are found in Table 1.

MIBK – March 2024 – Thushara Diyabalanage	
Comment Submitter: Alexandra Kowcz, MS, MBA; Industry Liaison to the Personal Care Council	
Date of Submission: March 13, 2024	
Comment	Response/Action
Discussion – The paragraph regarding use of MIBK as a denaturant is confusing. This paragraph should be revised to make it clear that 4% is the maximum concentration MIBK added to alcohol to denature it, so it is not orally consumed, rather than a maximum concentration in cosmetic products. It is not clear that “(that can be consumed)” is necessary. The purpose of a denaturant is to make alcohol unpalatable to drink. This should be clearly explained, or “that can be consumed” should be deleted as it suggests the denatured alcohol can be consumed.	Will be addressed in FAR.
The mode of action for the kidney tumors in rats should also be mentioned in the Discussion	Need the views of the Panel
Acute, Oral, old report summary; Short-Term, Oral, old report summary – Rather than “average lethal dose” it should be “median lethal dose”.	Will be addressed in FAR.
Subchronic, Inhalation, old report summary – “127 mg/MIBK for 4 h/day” is likely missing “m3 ” after the first ”/”	Will be addressed in FAR.
Occupational Exposure – Please correct “National Institute of Occupational Safety and Health” (“of” needs to be corrected to “for”)	Will be addressed in FAR.
The description of reference 19 still seems to be incomplete as no results for MIBK in urine are stated and it does not note whether the authors considered urinary MIBK as a useful biomarker for MIBK exposure. Although the ACGIH limit for MIBK may have been 50 ppm when the study was completed, it is currently 20 ppm, so it is confusing to state it is 50 ppm in the 2 paragraphs about this study when it is listed as 20 ppm earlier in this section.	Reference 19 indicates that there was significant presence of MIBK in the urine of the subjects. The authors do consider urinary MIBK as a useful biomarker for MIBK exposure. Need the views of the panel
The Summary states: “The TWA concentration of the urine of the workers...” this needs to be corrected as TWA generally refers to air concentrations.	Will be addressed in FAR.
In the footnote to the conclusion, it would be helpful to note that the use concentrations are found in Table 1	This is not our standard protocol. Does the Panel have any input?



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc., Senior Scientific Analyst/Writer, CIR
Date: March 18, 2024
Subject: Safety Assessment of Myristoyl Pentapeptide-4, Palmitoyl Pentapeptide-4, and Pentapeptide-4 as Used in Cosmetics

Please find attached comments received from the Personal Care Products Council on the Draft Report of the Safety Assessment of Myristoyl Pentapeptide-4, Palmitoyl Pentapeptide-4, and Pentapeptide-4 as Used in Cosmetics.



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 18, 2024

SUBJECT: Draft Tentative Report: Safety Assessment of Myristoyl Pentapeptide-4, Palmitoyl Pentapeptide-4, and Pentapeptide-4 as Used in Cosmetics (draft prepared for the March 2024 meeting)

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

Memo – In the memo, the maximum use concentration for Palmitoyl Pentapeptide-4 in face and neck products is incorrectly stated as 0.012%. It should be 0.0012%.

Chemistry – It would be helpful to note the sequences associated with the CAS numbers. Based on the technical names and CAS numbers included in the Dictionary, only Palmitoyl Pentapeptide-4 is associated with two sequences. Pentapeptide-4 and Myristoyl Pentapeptide-4 are only associated with the KTTKS sequence.

Non-Cosmetic Use – What species was used in the wound healing study?

Endocrine Activity – Usually test concentrations are given as lowest to highest concentration tested. The concentrations in the agonist assay are stated as 1×10^{-2} – 3.16×10^{-6} M (the highest concentration first). Are these values correct?

Summary – In the Summary, it would be helpful to state the two highest concentrations that resulted in cellular toxicity in the YES assay.

Draft Discussion – In what study was there an absence of endocrine activity at 0.12%? The concentrations tested in the Endocrine Activity section are all in the units of M. If different units are used in the Discussion, they should also be mentioned in the Endocrine Activity section.

Table 1 – As noted above, it should be made clear that the Dictionary only has two sequences for

Palmitoyl Pentapeptide-4. If the structures of the second sequence are left in Table 1 for Myristoyl Pentapeptide-4 and Pentapeptide-4, it should be made clear that PCPC does not have any suppliers selling these two ingredients with both sequences.



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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
Jinxiu Zhu, PhD, DABT, ERT, DCST, CIR Toxicologist
Date: March 18, 2024
Subject: Wave 2 - WVE's comments on Strategy Memo for Dibutyl Phthalate

The enclosed comments received from Women's Voices for the Earth (WVE), dated March 14, 2024, on the Strategy Memo for Dibutyl Phthalate are submitted for the Panel's review in this Wave 2 submission.

In their comments, WVE provided details about US State laws or legislation in progress aimed at prohibiting the use of Dibutyl Phthalate, Diethyl Phthalate, and/or Dimethyl Phthalate in cosmetics. WVE asked the Panel to draw a conclusion impartially, without being influenced by the viewpoints of manufacturers or the Personal Care Product Council (PCPC).

First, it is important to point out that the Panel's evaluation of ingredient safety is based on the scientific evidence available at the time, with a special emphasis on how ingredients are used in cosmetics. A key aspect of the assessment involves examining consumer exposure to the ingredients and the health risks that may arise from using cosmetic products. Therefore, the safety conclusions reached by the Panel are strictly related to the use of ingredients in cosmetics as per the "the present practices of use and concentration described in the safety assessment," with the scientific data being the sole foundation for these conclusions. The Panel does not engage in regulatory matters. Nonetheless, when specific ingredients appear on the EU Annex II list and/or are prohibited by US state laws, the Panel is keen to comprehend the foundation of such restrictions and the scientific evidence supporting these prohibitions.

Following a request from the US FDA, the Panel added Dibutyl Phthalate to the 2024 priority list. However, data from the 2023 FDA VCRP¹ and the PCPC survey² both indicated no instances of Dibutyl Phthalate being used in cosmetics; among the phthalates, PCPC has only provided use concentration data for Diethyl Phthalate. Accordingly, a strategy memo was submitted to the Panel during the original mailing for the March meeting, querying whether Diethyl Phthalate and Dimethyl Phthalate should be included in the rereview. That memo also included a risk assessment that utilizes use concentration data of Diethyl Phthalate across various cosmetic product categories for the Panel's deliberation. Additionally, it is worthwhile to mention that Dibutyl Phthalate and Diethyl Phthalate are commonly found in the environment. Beyond consumer products, humans are exposed to these chemicals from a variety of sources, such as plastics, food, and drinking water, etc.³⁻⁵ This widespread exposure has raised safety concerns regarding the cumulative effects from these various sources. However, the Panel's purview is to evaluate only the risks associated with the use of cosmetic products.

The Panel is requested to review WVE's comments and consider whether there is a need to discuss the potential concerns raised by such regulations in the report.

References:

1. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients (VCRP). In:2023.
2. Personal Care Products Council. Concentration of use by FDA product category: Phthalates. In:2023.
3. U.S. Centers for Disease Control and Prevention (CDC). Phthalates Factsheet.
https://www.cdc.gov/biomonitoring/Phthalates_FactSheet.html#:~:text=Phthalates%20are%20a%20group%20of,%20shampoos%20hair%20sprays). Updated 4/5/2021. Accessed 3/14/2024.
4. Agency for Toxic Substances and Disease Registry (ATSDR). ToxFAQs™ for Di-n-butyl Phthalate.
<https://wwwn.cdc.gov/TSP/ToxFAQs/ToxFAQsDetails.aspx?faqid=858&toxid=167#:~:text=Highlights,have%20been%20found%20in%20humans>. Updated 10/21/2011. Accessed 2/12/2024.
5. (ATSDR) ATSaDR. Public Health Statement for Diethyl Phthalate.
<https://wwwn.cdc.gov/TSP/PHS/PHS.aspx?phsid=601&toxid=112#:~:text=Diethyl%20phthalate%20can%20enter%20your,consumer%20products%20containing%20the%20substance>. Updated 10/21/2011. Accessed 2/12/2024.



March 14, 2023

Re: Comments on the Strategy Memo for Dibutyl Phthalate

To the CIR:

The strategy memo for dibutyl phthalate currently includes relevant regulatory information that in the EU, DBP is listed on Annex II, the list of substances prohibited in cosmetic products.

The memo is lacking information, however, about recently passed U.S. State laws which also prohibit DBP and in some cases DEP and DMP from use in cosmetics, which go into effect as early as January 1, 2025.

Specifically,

California passed AB496 which bans DBP from cosmetics and goes into effect January 1, 2025.

Text of bill: https://leginfo.legislature.ca.gov/faces/billTextClient.xhtml?bill_id=202320240AB496

It is worthwhile noting that industry supports U.S. alignment with the EU Annex II list – and did not oppose the inclusion of DBP in this bill stating:

“The undersigned organizations (the Personal Care Products Council, Fragrance Creators Association, California Chamber of Commerce, and other industry groups) support better alignment with the health and safety standards set forth by the European Union that prohibit the intentional use of specified ingredients which are listed in the EU Cosmetics Regulation 1223/2009, ANNEX II, List of Substances Prohibited in Cosmetic Products.”

Similarly, **Maryland** passed 21-259.2 which also bans DBP from use in cosmetics and goes into effect on January 1, 2025.

Text of bill: <https://mgaleg.maryland.gov/mgaweb/site/laws/StatuteText?article=ghg§ion=21-259.2&enactments=false>

This Maryland bill was supported by the Personal Care Products Council.

Text of PCPC support letter: https://mgaleg.maryland.gov/cmte_testimony/2021/hgo/15DRWk-CsGDCn2CMKrsSNfyL2peuf2gwH.pdf

Washington State passed Substitute House Bill 1047 which bans the class of orthophthalates from use in cosmetics. The class of orthophthalates include DBP, DEP and DMP.

This law also goes into effect January 1, 2025.

Text of bill: https://www.bdlaw.com/content/uploads/2023/06/1047-S.SL_.pdf

Similarly, **Oregon** passed SB546 which bans the class of orthophthalates from use in cosmetics. The class of orthophthalates include DBP, DEP and DMP. This law goes into effect January 1, 2027.

Text of bill: <https://olis.oregonlegislature.gov/liz/2023R1/Downloads/MeasureDocument/SB546/Enrolled>

Of course, whether or not manufacturers and/or the PCPC approve of the prohibition of a chemical from cosmetics should have no bearing on the Expert Panel's assessment of the science. If an ingredient is unsafe, it must be declared so, even if manufacturers and the PCPC strongly wished to continue using it. It must be declared unsafe no matter how uncomfortable making that assertion may be for Expert Panel members. **In this case, it may be helpful for Expert Panel members to know that in stark contrast to positions held when the Panel last reviewed the safety of phthalates, there has been little if any industry opposition currently to bans of phthalates from cosmetics in state legislation.**

Also – of note – there are a number of pending bills currently working their way through state legislatures in 2024-25, which also aim to prohibit the use of phthalates from use in cosmetics. Such as:

Pending legislation in **Georgia** would ban DBP and DEP from use in cosmetics.

Text of Bill: <https://www.legis.ga.gov/legislation/64348>

Pending legislation in **Illinois** would ban DBP from use in cosmetics.

Text of Bill:

<https://ilga.gov/legislation/fulltext.asp?DocName=&SessionId=112&GA=103&DocTypeId=HB&DocNum=1282&GAID=17&LegID=143392&SpecSess=&Session=>

Pending legislation in **New York** would ban DBP and DEP from use in cosmetics, and another bill would ban DBP from use specifically in nail products.

Text of Bills:

https://nyassembly.gov/leg/?default_fld=&leg_video=&bn=A06969&term=2023&Summary=Y&Text=Y
and
<https://nyassembly.gov/leg/?bn=A787&term=2023>

Pending legislation in **New Jersey** would ban DBP from use specifically in nail products.

Text of Bill: https://pub.njleg.state.nj.us/Bills/2024/A2000/1775_11.PDF

Pending legislation in **Vermont** would ban orthophthalates (DBP and DEP) from use in cosmetics.

Text of Bill: <https://legislature.vermont.gov/bill/status/2024/H.544>

Pending legislation in **Maine** would ban DBP and DEP from use in cosmetics, Text of Bill:

http://www.mainelegislature.org/legis/bills/display_ps.asp?id=1908&PID=1456&snum=131

Thank you for your consideration of these comments.



Alexandra Scranton
Director of Science and Research



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc., Senior Scientific Analyst/Writer, CIR
Date: March 18, 2024
Subject: Amended Safety Assessment of *t*-Butyl Alcohol as Used in Cosmetics

Please find attached comments received from the Personal Care Products Council on the Amended Safety Assessment of *t*-Butyl Alcohol as Used in Cosmetics.



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 18, 2024

SUBJECT: Draft Report: Amended Safety Assessment of t-Butyl Alcohol as Used in Cosmetics (draft prepared for the March 2024 meeting)

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

Key Issue

Introduction – The 1% t-Butyl Alcohol concentration used in the DART study was in a liquid diet. The Introduction should not state that this is “comparable” to use of 1% BHT in a cosmetic product. To compare the dietary use to cosmetic use mg/kg/day doses need to be calculated for each exposure. Unless the liquid dietary study measured how much diet was consumed, calculating dose is not possible because consumption values for a standard diet do not apply.

Additional Considerations

Throughout the report, “ α 2 μ -globulin” needs to be corrected to “ α 2u-globulin” (“ μ ” symbol should be the letter “u”)

Natural Occurrence – If available, information on the concentrations of t-Butyl Alcohol found in food should be stated.

ADME, old report summary – Since the rest of the ADME section discusses how t-Butyl Alcohol is metabolized, perhaps calling it a “nonmetabolizable alcohol” should be deleted from the first paragraph. Saying that it not a substrate for alcohol dehydrogenase and catalase should be sufficient.

ADME, Oral, old report summary – The partition coefficients should not be in the oral section. It would be more appropriate to include them in the first paragraph of the ADME section. Please delete “liquid/air partition coefficient” as the value will depend on the identity of the liquid.

The following sentence does make sense: “t-Butyl alcohol was conjugated to a large extent with

glucuronic acid, and glucuronides in urine.” (glucuronic acid conjugates are glucuronides, maybe “are excreted” is missing after “glucuronides”).

ADME, Oral; Summary – The paragraph describing the rat study (reference 10) does not make sense as it says that t-butyl alcohol glucuronide is both a major and minor metabolite in rats. The paragraph describing this study in the Summary has more information. It also includes a summary of a metabolism study done in one person (male). t-Butyl Alcohol glucuronides were major metabolites in rats, but minor metabolites in the one human subject that was studied. The human study mentioned in the Summary needs to be added to the ADME section.

ADME, Inhalation, old report summary – The intraperitoneal study does not belong in the inhalation section. For the inhalation studies, please include the hours/day the animals were exposed. If available, some quantitative results should be added for reference 11 (inhalation pharmacokinetic study in rats).

Acute, Dermal, old report summary – Although it may have been presented under acute dermal toxicity in the original report, the first rabbit study in which the results only concern dermal irritation should be moved to the Dermal Irritation section.

Acute, Inhalation, old report summary – How many hours were the rats exposed to 10,000 ppm t-Butyl Alcohol in the first study described in this section?

Chronic, Oral, old report summary – As mg/kg doses are stated rather than drinking water concentration, it should state “in drinking water at doses of” (not “concentrations”).

DART, Animal, old report summary – The description of the methods suggests that all offspring were moved to surrogates, while the results suggests that only some of the offspring were moved to surrogates. Please revise the methods so it is consistent with how the study was conducted.

Endocrine – Please identify the “test article” rather than saying “test article”.

Occupational Exposure – The NIOSH concentration immediately dangerous to life or health (IDLH) has been updated, it is now 1,600 ppm not 8000 ppm as stated in the old report. The old value should not be presented in the new report. The current short-term exposure limit (STEL: 150 ppm, 450 mg/m³) should also be stated.

Exposure Assessment – The MoS calculation does not belong in the Exposure Assessment section. What were the effects observed at the LOAEL? Why was the NOAEL of 195 mg/kg/day selected?

Risk Assessment – It is not clear what this risk assessment represents. Is it the risk assessment that was included in RIFM’s publication? EPA does not develop Reference Doses (RfD) for cancer endpoints. The most current IRIS summary (updated in 2021 https://iris.epa.gov/ChemicalLanding/&substance_nmbr=1036) has an oral RfD of 0.4 mg/kg/day based on urinary tract effects and for cancer (oral exposure), a slope factor of 5 x 10⁻⁴ per mg/kg-day based on increasing thyroid tumors in mice is stated.

Summary – Please state that the 1% concentration used in the DART study was in a liquid diet.

Table 5 – The column headings should be clearer on which columns represent product exposure and which columns represent Ingredient exposure.

Rather than mostly relying on the SCCS Notes of Guidance for product exposure, it would be helpful to use the following RIFM paper which more clearly identifies the sources of the values used (see Table 3 of this paper).

Api AM, Basketter DM, Cadby PA, et al. 2008. Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. *Regul Tox and Pharm* 52: 3-23.

Table 5 should note that the Daily Exposure by Product Category from the SCCS Notes of Guidance include the retention factors. If product use values are obtained from other sources, retention factors should also be applied. For example, based on the SCCS Notes of Guidance (and the Api et al. 2008 paper), hair styling products have a retention factor of 0.1, which would result in the exposure from hair spray to be reduced to 500 mg/day compared to 5000 mg/day (the value in the table). The table should note the percentile level for the values from CTFA habits and practices studies.

Unless it is known that it is a facial moisturizer, exposure amounts for body lotion should be used for moisturizers.

Products defined as “other” means it does not fit into the existing FDA cosmetic product categories. Thus, either the product should be defined, and exposures referenced, or exposure cannot be estimated for these products. In the latter, the exposure would need to be within the exposures encompassed elsewhere in the table to be considered “safe as used”. In Table 5, exposure should not be estimated for the “other skin care preparations” containing 0.01% t-Butyl Alcohol.



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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 Writer/Analyst, CIR
Date: March 18, 2024
Subject: Wave 2 - Comments on the Draft Amended Report (DAR) on Toluene

Attached are comments (*WVEcomments_Toluene_Wave2_032024*) received from Women's Voices for the Earth (WVE) on March 13, 2024, on the DAR on Toluene.

These comments suggest the inclusion of each product category that is listed for Toluene in the California Safe Cosmetics Program (CSCP) Product Database (anti-wrinkle/anti-aging products, artificial nails and related products, basecoats and undercoats, blushes, etc.) into the report. WVE also suggested that the Panel should take into account California's Department of Toxic Substance Control's (DTSC) updated regulation (effective on July 26, 2023) on the use of Toluene in nail products. This regulation states the requirements "*a manufacturer must meet to demonstrate and certify that the concentration of toluene in a Priority Product they make does not exceed the Alternatives Analysis Threshold of 100 parts per million (ppm).*"

It is important to note that the CSCP database provides dates that products containing Toluene were discontinued, and dates in which Toluene was removed from the product formulation. When preparing the DAR, CIR staff noted that numerous products reported to contain Toluene in the CSCP database were either flagged as having the ingredient removed or flagged for being discontinued. For example, the database lists products containing Toluene that are applied to the eye area (e.g., eye shadow, eyeliner/eyebrow products), along with the date in which Toluene was removed from these product formulations. As Toluene is no longer used in the formulation of many of these products on the current market, it is unnecessary to add this category of information, or the related concentration data, to the report. Similarly, all *Lip Gloss/Shine (powder)* products are marked as "Ingredient Removed Date 4/24/2020," with *Lip Gloss/Shine (liquid)* being the only exception. Nevertheless, this information has been included in the DAR, as shown below:

In addition, according to the California Safe Cosmetics Program Product Database, Toluene is also used in lip glosses at concentrations of 0.00005% (which may result in incidental ingestion; database updated in 2024). This database also reported the use of Toluene in perfumes at up to 0.0042%. (pdf page 25 in the DAR. Many lip glosses in the database are not currently reported to be in use; however, for the lip gloss that is reported to be in use, no concentration of use is reported. Therefore, a previous concentration of Toluene in lip gloss is reported in this statement.)

Other Toluene-containing products that are marked as discontinued in the database include, but are not limited to, anti-wrinkle/anti-aging products, skin toners, sunscreen, and suntan enhancers. It is also important to note that some product categories in the database have the concentrations of Toluene listed as either 0, or left blank. As a result, it remains unclear whether Toluene is still being formulated in these products.

Regarding California DTSC's regulation on nail products containing Toluene, it should be noted that California's DTSC's Safer Consumer Products (SCP) regulatory framework **is not based on quantitative risk assessment**.¹ According to the SCP Regulations, DTSC considers two primary factors when identifying product-chemical combinations:

- The potential for exposure to the Candidate Chemicals in the product
- The potential for that exposure to cause significant or widespread adverse impacts

The California DTSC also states that in addition to the primary factors specified in the SCP regulations, DTSC decisions are also based on several policy considerations including "*Whether naming a Priority Product will meaningfully enhance protection of public health or the environment, **beyond the protections provided by existing laws and regulations.***"

Additionally, the following statements regarding DTSC's amendment to the regulation listing Nail Products Containing Toluene as a Priority Product² are quoted below for the Panel's consideration:

On July 26th, 2023, the Office of Administrative Law approved DTSC's amendment to the regulation listing Nail Products Containing Toluene as a Priority Product. The amendment, initiated by DTSC on January 20, 2023, establishes the requirements that a manufacturer must meet to demonstrate and certify that the concentration of toluene in a Priority Product they make does not exceed the Alternatives Analysis Threshold of 100 parts per million (ppm). This regulation became effective on July 26th, 2023.

Pregnant nail technicians and their fetuses are especially sensitive to adverse impacts of toluene exposure from nail products. Infants and children of nail technicians often accompany their parents to the workplace and may be exposed to toluene-containing nail products. Infants and young children are more susceptible than adults to adverse impacts from toluene due to physiological differences.

Based on the criteria in the SCP Regulations, we have determined that exposure to toluene through normal use of nail products may contribute to or cause significant or widespread adverse impacts to Californians, including sensitive subpopulations such as nail salon workers, pregnant women and their fetuses, infants, children, and adolescents. Toluene has been detected in air in nail salons at levels above California regulatory standards. Nail technicians (also known as manicurists) have an especially high potential for toluene exposure due to their longer workdays and workweeks compared to employees in other sectors; they are often not provided with adequate information concerning chemical safety; they are often not provided with proper personal protective equipment (PPE); and their workplaces often lack appropriate ventilation.

CIR Staff is requesting that the Panel review the comments from WVE, as well as the California DTSC's determination of listing nail products containing Toluene as a Priority Product. The Panel is also requested to determine if there is a need to discuss California's regulation on nail products containing Toluene in the report.

Separately, comments on the DAR submitted by Council (PCPCcomments_Toluene_Wave2_032024) are enclosed.

References

1. California Department of Toxic Substances Control. Priority Products. <https://dtsc.ca.gov/scp/priority-products/#:~:text=According%20to%20the%20SCP%20Regulations,significant%20or%20widespread%20adverse%20impacts>. Published 2024. Updated 2024. Accessed March 14, 2024.
2. California Department of Toxic Substances Control. Effective January 1, 2023: Nail Products Containing Toluene. Published 2024. Updated 2024. Accessed March 14, 2023.

March 13, 2024

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

To the CIR,

I am writing to provide the following comments on the amended safety assessment of Toluene as Used in Cosmetics.

- There is additional relevant data on toluene-containing cosmetic products from the California Safe Cosmetics Database that is not reflected in the current draft.
- There is a significant new regulation in California restricting toluene use in nail products to 100ppm that should be included in the draft.
- If the CIR panel concludes "safe as used" for toluene it must clarify how and why their conclusion differs significantly from the conclusion of the CA DTSC which stated:
- *"...we have determined that **exposure to toluene through normal use of nail products may contribute to or cause significant or widespread adverse impacts to Californians, including sensitive subpopulations such as nail salon workers, pregnant women and their fetuses, infants, children, and adolescents.**"*

1) California Safe Cosmetics Database Data on Toluene in Cosmetics

I was pleased to see the inclusion of data from the California Safe Cosmetics Database on cosmetic products containing toluene. The database is an excellent source of additional information on ingredients in products, especially given the limitations of the now-discontinued VCRP. However, it appears that the CIR panel has not been given all the information that the database has to offer. The current draft states:

"According to 2023 concentration of use data, Toluene is used in baby lotions/oils/creams at up to 0.000001%.⁹ In addition, according to the California Safe Cosmetics Program Product Database, Toluene is also used in lip glosses at concentrations of 0.00005% (which may result in incidental ingestion; database updated in 2024).¹¹ This database also reported the use of Toluene in perfumes at up to 0.0042%."

It is worth noting however that unlike the VCRP data which reported 0 uses of toluene, there are over 260 products entries in the California database. The database reported many different types of products containing toluene including:

- Anti-Wrinkle/Anti-Aging Products (making a cosmetic claim)
- Artificial Nails and Related Products
- Basecoats and Undercoats
- Blushes
- Body Washes and Soaps
- Eye Shadow
- Eyeliner/Eyebrow Pencils
- Face Powders

- Facial Masks
- Lip Gloss/Shine
- Nail Polish and Enamel
- Nail Polish and Enamel Removers
- Other Nail Products
- Other Personal Care Product
- Other Shaving Product (Shave Foam)
- Other Skin Care Product
- Perfumes - Oils and Lotions
- Perfumes - Solids and Powders
- Perfumes/Eaux de Parfum
- Scrubs and Exfoliants
- Skin Cleansers
- Skin Moisturizers (making a cosmetic claim)
- Skin Toner (making a cosmetic claim)
- Sunscreen (making a cosmetic claim)
- Suntan Enhancers
- UV Gel Nail Polish

It is unclear why the draft assessment did not include mentions of many of these categories as many of them imply a different kind of exposure than just nail products, and many of them could be used simultaneously leading to cumulative exposure to toluene.

It may be helpful for the CIR staff to provide the panel with the full list of products (and concentrations where available) listed in the California Safe Cosmetics Database.

- 2) California Regulation on Toluene in Nail Products as of July 26, 2023 should be included in the safety assessment.

On July 26, 2023, a new California regulation on toluene in nail products went into effect. Details can be accessed here: <https://dtsc.ca.gov/scp/nail-products-containing-toluene/>

Specifically, the California Department of Toxic Substances Control (DTSC) now requires manufacturers of nail products to certify that their products **do not contain more than 100ppm of toluene**. If a manufacturer makes a product that exceeds that threshold – they must either report their intent to remove the product from the market, remove the chemical from the product or produce an alternatives assessment analysis to identify alternatives for the product.

This regulation was based upon the conclusion of the California DTSC's analysis of toluene in nail products which states:

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

This highly relevant regulation should be mentioned in detail in the safety assessment.

- 3) In addition, **if the CIR Expert Panel's conclusion is significantly different from the conclusion of the DTSC, this should be explained and justified in the safety assessment as well** – seeing as the two safety assessments are based largely on the same scientific data.

Thank you for your consideration of these comments.

Sincerely,

A handwritten signature in dark ink, appearing to read "Alexandra Scranton", written on a light-colored background.

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



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 18, 2024

SUBJECT: Draft Report: Amended Safety Assessment of Toluene as Used in Cosmetics
(draft prepared for the March 2024 meeting)

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

Key Issues

The Impurities summary from the original report states: "Toxicological and clinical studies involving Toluene should specify the purity of Toluene used for experimentation to determine if observed effects were caused by Toluene, and not benzene as an impurity." It would have been helpful if this advice had been followed and impurities of the material tested stated in the CIR report for each study reviewed. For example, in some studies, NTP tested technical grade Toluene, while the Toluene tested was 99% pure in other NTP studies.

The study from which the NOAEL (used in the risk assessment) was derived should be described somewhere in the CIR report. The report should also state why the NOAEL of 625 mg/kg/day was selected for use in the risk assessment. What effects were observed in the study that identified this NOAEL? Is it really the most appropriate value as developmental and neurotoxic endpoints are generally considered the most sensitive endpoints for Toluene toxicity?

For inhalation studies, in addition to exposure concentration, the hours/day and days/week of exposure always needs to be stated.

Additional Considerations

Chemical Properties – The following does not belong in the Chemical Properties section: "systemic exposure resulting from topical application cannot be easily mitigated."

Reactivity, old report summary – In the following, please correct "silica tube filled with porcelain chips at Toluene at 700°C" (it would make more sense if "at Toluene" was deleted).

Cosmetic Use – The low levels of Toluene in multiple product categories reported in the PCPC concentration of use survey are residual concentrations not intentionally added Toluene that has a function in the product. Rather than saying that Toluene “is used” in cosmetic products at the low levels, it would be better just to state it is in products at the reported low concentrations.

Cosmetic Use Exposure – Something is missing from the following: “within a 16 m³ [?] that maintained an air flow” (perhaps “chamber” needs to be added)

Cosmetic Use Exposure – Is reference 14 (SCCS 2006 Opinion [should be 2008]) the correct reference for the study in 178 nail technicians? What was the time-frame the air concentrations of Toluene were measured?

ADME, old report summary – Please revise: “Urine of humans exposed to 50 and 800 ppm Toluene for 8 hr contained 59% hippuric acid and 41% benzoyl glucuronide.” It is not clear what the percentage values represent, as it is written it is the urine, but it is more likely either the percentage of the administered dose or the percentage of total metabolites found in the urine.

Please identify the substance that had a peak blood level of 14 µg/g about 1 hr after administration.

Subchronic and Chronic – Please be more specific about what was observed at which doses. For example, the following sentence suggests that deaths were observed at 312 mg/kg/day, but 625 mg/kg/day was chosen as the NOAEL for risk assessments. “Studies performed in mice and rats given Toluene (312-5000 mg/kg/d; in corn oil; 13 wk) via gavage resulted in death; increases in organ weights (e.g., liver, kidney, heart) dose-dependent necrosis of the brain, and hemorrhage of the urinary bladder.”

DART – The hazard classifications and Proposition 65 safe harbor values (first paragraph after the old report summary) do not belong in the DART section. It should be noted that the 7000 µg/day value is for oral exposure. California also has a 13,000 µg/day value for inhalation exposure. It should be made clear that if exposure to Toluene from a product is below these levels, the product is exempt from Proposition 65 requirements.

What was the route of exposure used in the study in which rats were exposed to 5 or 50 ppm Toluene (presumably this is an inhalation study)? How many hours/day were the rats exposed?

Genotoxicity; In Vitro Skin Viability Following Exposure to Toluene Vapor; Summary; Table 6 – Rather than saying a concentration of 1,000,000 ppm was used in the study using skin disks, it should state that undiluted Toluene was used (1,000,000 ppm is 100%). It should also be made clear that in this study the skin was not directly exposed to Toluene. It was exposed to Toluene vapor from various concentrations of Toluene that were added in the chamber with the skin. Unless it is somewhere else in the paper, the vapor concentrations of Toluene to which the skin was exposed were not stated. How this study was conducted is not clear in Table 6.

Genotoxicity; Table 6 – The mice in the NTP micronucleus assay (reference 51) were exposed by gavage (stated in G04 - In Vivo Micronucleus Summary Data on the NTP website). It should

not state: “method of administration not stated”. The CIR report should also note that technical grade Toluene was used in this study.

Carcinogenicity, old report summary – Please add information about the doses used in the described studies.

Effects on Respiratory Tract – “neutrophins” needs to be corrected to “neurotrophins”, and “Neutophin-3” needs to be corrected to “Neurotrophin-3”

Bone Mass Toxicity – Please check the bone mineral density and bone mineral content values. Currently it states: “Bone mineral density and bone mineral content were determined to be $0.008 \pm 0.005 \text{ g/cm}^2$ and $0.11 \pm 0.006 \text{ g}$ in the treated group, respectively, and 0.19 ± 0.007 and $0.020 \text{ g/cm}^2 \pm 0.009 \text{ g}$ in control animals, respectively. Bone mineral density and bone mineral content were significantly lower in treated versus control groups ($p < 0.05$).” In addition to the units being in the wrong place, if the values are in the order bone mineral density followed by bone mineral content, the treated value for bone mineral content (0.11) is not lower than the control value for bone mineral content (0.02) as stated in the second sentence.

Toluene Abuse – Were there any estimates of doses/concentrations of Toluene that resulted in fatalities?

Immunotoxicity – It is not clear why reference 84 needs to be in a separate section. This study could be presented in the acute toxicity section as they look at more than just immunotoxicity markers. The word “mice” needs to be added after “male Swiss-Webster”.

Dermal Irritation and Sensitization, old report summary – If there were only 4 skin irritation studies in rabbits, rather than saying that a majority were conducted under occlusive conditions, please be more specific and say (if correct) 3 of 4 studies were conducted under occlusive conditions.

Case Reports, Occupational – Is the age of the subject in reference 95 correct? Thirty-eight seems early to retire.

Occupational Toxicity/Epidemiology/Case Reports – Please state the material the gasoline workers were exposed to at 60.3 and 527 ppb.

Occupational Exposure Limits – As some of the values in Table 9 are not regulations, they should not be called “regulations” in the text.

Toxicity Values and Minimal Risk Levels – In the description of these values, it would be helpful note the endpoint of concern observed at the LOAEL (or LOAEC).

Margin of Safety Calculation, Tier 2 – This is not a “probabilistic approach” for exposure assessment. If it was a probabilistic approach, there would be a range of exposures based on, for example, variable concentrations of Toluene in products and variable use amounts.

Margin of Safety Calculation, Tier 3 – It is not clear why the exposure values determined in reference 3 were not used (as stated in the Cosmetic Use section these were 2160, 28,200, and 7760 µg/day for salon patrons, nail technicians and home users).

Summary – In the description of the 2-year carcinogenicity bioassay it states that “no neoplasms were observed”. This is unlikely. It is more likely that neoplasms were not significantly increased in treated animals compared to controls.

Table 9 – It should be made clear that the Proposition 65 MADLs are not occupational exposure limits. They are the exposures at which product labeling with Proposition 65 warnings are required.

Reference 14 – The date of the SCCS opinion should be 2008 not 2006.

Review of Additional References

In general, the following types of references should always be included in CIR reports.

1. Human ADME studies, including PBPK models
2. Human exposure studies looking for adverse effects
3. Studies in monkeys (especially if they include multiple doses/exposure concentrations)
4. Multi-generation studies
5. The most recent IARC review
6. Studies done by NTP

For Toluene, additional studies/reviews of developmental effects and neurotoxicity that look for doses/concentrations that do not cause these effects would be helpful.

Based on the titles and abstracts these are the additional studies that may be useful to add to the CIR report (in the same order as they were presented in the list).

Kezic et al. 2000

Thrall et al. 2002 (2 studies, one human one rat dermal absorption of vapor PBPK models)

McDougal et al. 1990

Baelum et al. 1993

Anderson et al. 1983 (human exposure study)

Donald et al. 1991 (DART review, especially interested if it discusses NOAELs)

Wilkens-Haug et al. 1997 (DART review, especially interested if it discusses NOAELs)

Roberts et al. 2003

DaSilva et al. 1991

Richer et al. 1993

Weiss et al. 1986

IARC 1999

Bukowski 2001

Taylor et al. 1985

Hyden et al. 1983

Bushnell et al. 2007



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Bart Heldreth, PhD, Executive Director, CIR
Date: March 18, 2024
Subject: Procedures of the Read-Across Working-Group

With the first meeting of the Read-Across Working-Group (RAWG) occurring at this meeting, it may be useful to review what the [Cosmetic Ingredient Review Procedures & Support to the Expert Panel for Cosmetic Ingredient Safety](#) have to say about such a team. Addressed as “working teams” therein, the procedures of this team are outlined in Section 43, starting at page 17 (pdf page 18), and are excerpted as follows:

Section 43. Working Teams of Expert Panel Members.

Working teams of Expert Panel members may be designated to review information, to prepare draft documents, or to undertake other specific assignments for the Expert Panel, subject to the following conditions:

(a) The Chair of the Expert Panel may appoint working teams comprised of from two to four members of the Expert Panel (one of whom may be the Chair of the Expert Panel) to review information about designated ingredients, to prepare draft documents for consideration by the entire Expert Panel, or to perform other specific assignments for the Expert Panel. The Chair of the Expert Panel shall assign a leader for each working team.

(b) A meeting of a working team is not a meeting of the Expert Panel and shall be governed by the procedures established by this Section and not by the procedures applicable to meetings of the Expert Panel.

(c) A working team shall meet at the call of its leader, issued through the Executive Director. A working team may meet in Washington, DC, at another location if that location is more convenient for the working team members and conserves the resources of the CIR, or may meet via electronic means. Liaison representatives shall be advised of all working team meetings and may attend and participate. Anyone may attend working team meetings.

(d) Any document distributed by a working team member to other members of the team, including a call for meeting issued by the team leader, shall be distributed through the Executive Director, who shall simultaneously send the document to the liaison representatives. The Executive Director shall maintain a log and copies of all such documents.

(e) A working team may be assisted by the CIR staff, through the Executive Director. The CIR staff shall be responsible for maintaining minutes of all working team meetings.

(f) A document prepared by a working team may be submitted to the Expert Panel by the leader of the working team, through the Executive Director. The Executive Director shall promptly distribute the document to Expert Panel members and to liaison representatives. Such a document should be received by Expert Panel members and liaison representatives at least two weeks before the Expert Panel meeting at which it is to be voted upon or otherwise considered.

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(g) A working team document submitted to the Expert Panel is not a document of the Expert Panel unless and until the Expert Panel approves it. The Expert Panel may approve a working team document with or without revisions, may return the document to the working team for additional work consistent with the directions of the Expert Panel and the procedures described above, or may disapprove the document.

(h) Liaison members may describe to their constituencies the substance of a working team document, but may not quote from the document or make it available for reading or reproduction unless and until it is submitted to the Expert Panel and thereby becomes available for public disclosure. When a working team submits a document to the Expert Panel, the document becomes subject to the provisions of these procedures governing public availability of documents submitted to the Expert Panel and thereby becomes available for public disclosure in accordance with Section 51 of these procedures.