ADMIN

CIR SSC Risk Comments Exposure SM

EXPERT PANEL MEETING
March 28-29, 2024

Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Jinqiu Zhu, PhD, DABT, ERT, DCST, CIR Toxicologist
Date: March 4, 2024
Subject: CIR SSC's Comments on Quantitative Systemic Risk Assessments and Models Used in Draft Systemic Quantitative Risk Assessments

The CIR Science and Support Committee (SSC) of the Personal Care Products Council submitted comments on Quantitative Systemic Risk Assessments and Models Used in Draft Systemic Quantitative Risk Assessments (*CIRSSC_risk_032024*).

In the comments, the CIR SSC proposes that a quantitative systemic risk assessments might not be useful in most CIR report, but emphasizes the necessity of incorporating transparent exposure assessments (for both systemic and dermal exposure) whenever possible. Moreover, they consider that although calculating a margin of safety (MoS) may not be essential for completing every CIR safety assessment; such calculations are warranted when an exposure assessment has been completed and an experimentally derived NO(A)EL (or LOAEL) has been identified. The CIR SSC advocates for the use of VERMEER Cosmolife for exposure estimation, highlighting that the tool's exposure parameters are derived from SCCS Note of Guidance (NoG);[1] however, they advise against using the integrated CORAL model for NOAEL prediction because the model relies on a limited training set and is not appropriate for a definitive risk assessment, beyond that training set. Furthermore, the CIR SSC believes other in silico models, such as the OECD toolbox, are also not yet valid for identifying NO(A)ELs for quantitative risk assessments; instead, it is preferred to identify NOAELs (and LOAELs) based on the data presented in the report.

To demonstrate their notion that inclusion of a quantitative systemic risk assessment in CIR reports should be considered on a case-by-case basis, the CIR SSC cites Copper Gluconate as an example, highlighting that copper is an essential element and noting that other gluconates have previously been reviewed by CIR. Accordingly, the risk assessment section in the report (*report_CopperGluconate_032024*) has been updated by comparing the exposure levels of copper resulting from cosmetic use with the daily copper intake limit established by National Institutes of Health (NIH).

Likewise, when assessing risk for the use of BHA (*report_BHA_032024*), an exposure assessment across various cosmetic product categories was performed; the level of exposure was then compared to the acceptable daily intake (ADI) set by European Food Safety Authority (EFSA), as BHA is an authorized food additive in the EU. In this case, a quantitative systemic risk assessment is not appropriate and was not performed.

In their comments, the CIR SSC references Octoxynols as an additional example, to illustrate a systemic quantitative risk assessment is not always appropriate. In this example, *irritation is generally the main concern for surfactants and local effects are more likely to be the endpoint of concern rather than systemic toxicity*.

Furthermore, the CIR SCC recommends utilizing additional sources beyond the SCCS NoG to identify exposure parameters, while also clarifying each value used in the exposure assessment. In the exposure assessment sections of the draft reports provided for the March 2024 meeting, CIR staff did retrieve exposure parameters for a variety of product categories from an extensive selection of data sources as needed. These include SCCS NoG,[1] PCPC habits and practices data,[2] EPA exposure factors handbook,[3] RIFM exposure models,[4] and other relevant peer-reviewed articles.[5] Importantly, the CIR SSC highlighted that *if the literature contains measurements of actual exposure, the measured values should be used rather than estimated values.* In light of such comments, CIR staff propose a draft tiered approach (*report_Toluene_032024*) for estimating Toluene exposure from nail polish products use; e.g., in the third tier of the risk assessment, the measurement of Toluene exposure in the breathing zone of 15 female subjects under simulated-use conditions (unpublished study submitted by the Council in 1991)[6] was considered rather than relying on the Danish EPA's estimation of the inhalable fraction of formaldehyde as used in the second tier of risk assessment).

The CIR SSC also comments that *exposure should be estimated for high exposure products, e.g., products intended to be used on a large surface area of the body, not just the products with the highest reported use concentrations*. This matter has been discussed in a strategy memo (*strategymemo_Exposure_032024*) submitted separately to the Panel. It is important to understand that in certain situations, products intended for application on whole body areas could possibly still lead to relatively lower exposure

compared to those applied to smaller regions, such as the hands or face. This is due to the impact of other exposure parameters, like the retention factors and maximum concentration of use, which also play a significant role in determining the overall systemic exposure dose.

The Panel is being asked to consider the CIR SSC's comments in the submission and to take into account their recommendations for carrying out exposure and quantitative risk assessments as part of the report evaluation process.

References:

1. Scientific Committee on Consumer Safety (SCCS). The SCCS's notes of guidance for the testing of cosmetic ingredients and their safety evaluation (12th Revision). 2023. SCCS/1647/22.
2. CTFA (currently known as Personal Care Product Council). Unpublished data regarding average hairspray and perfume use. In:2002:3.
3. U.S. Environmental Protection Agency (EPA). Exposure Factors Handbook (2011 Edition)- Dermal Exposure Factors. https://www.epa.gov/sites/default/files/2015-09/documents/efh-chapter07.pdf. Updated 11/08/2023. Accessed 01/12/2024.
4. Api AM, Basketter D, Bridges J, et al. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Regul Toxicol Pharmacol. 2020;118:104805.
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6. Bio-Research Laboratories Ltd. Estimation of toluene concentrations in the breathing zone of woman subjects following exposure to nail polish products under simulated use conditions. In:1991.

Personal Care Products Council
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TO: Bart Heldreth Ph.D., Executive Director – Cosmetic Ingredient Review
Expert Panel for Cosmetic Ingredient Safety

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: February 7, 2023

SUBJECT: Quantitative Systemic Risk Assessments and Models Used in Draft Systemic Quantitative Risk Assessments

The CIR Science and Support Committee (CIR SSC) appreciates the opportunity to comment on draft quantitative risk assessments included in CIR reports and on the models used to prepare the draft quantitative risk assessments.

Review of Draft Quantitative Systemic Risk Assessments

We carefully reviewed the quantitative systemic risk assessments included in the draft Octoxynol report and the Scientific Literature Review on Copper Gluconate. It is not clear why a systemic quantitative risk assessment needs to be completed for Octoxynols, as irritation is generally the main concern for surfactants and local effects are more likely to be the endpoint of concern rather than systemic toxicity. Copper, a component of Copper Gluconate, is an essential element and other gluconates have been reviewed by CIR and found safe for use in cosmetics. It does not seem necessary to conduct a systemic risk assessment for Copper Gluconate. A comparison of exposure to copper from cosmetics containing Copper Gluconate to the recommended daily allowance or the tolerable upper intake level may be a more useful exercise to provide perspective on exposure to copper from cosmetics.

As part of the draft quantitative systemic toxicity risk assessments included in CIR reports, the VERMEER Cosmolife tool was used to estimate exposure to an ingredient from use in cosmetics. This tool uses SCCS Notes of Guidance (10th and 11th revisions) values to complete the exposure calculations. It appears to be a useful tool to estimate exposure. In the examples reviewed, exposure was estimated only for the high concentration products. Clear descriptions of the sources of the parameters used to estimate exposure were not always included in the CIR report. For example, Copper Gluconate exposure from a baby shampoo was estimated. Although the body weight of a child was used in the calculation, the surface area of 1440 cm^2 was used. SCCS notes of guidance indicates that this value represents the area of the hands and half the area of the head of an adult.

We are more concerned about the use of the CORAL model to predict a NOAEL. As indicated in the Toropov et al. 2015[1] paper and Selvestrel et al. 2021[2] papers, this model is based on 140 organic chemical structures from US EPA's Integrated Risk Information System (IRIS) database, the Hazard Evaluation Support System (HESS) and Munro databases. In Selvetrel's opinion, this model was not ready for use in definitive risk assessments. He states: "An example of an endpoint with higher uncertainty is the predictive tool for NOAEL, which is a difficult endpoint because it is affected by natural variability and by the choice of the doses within the experimental test. The current version of the model is based on a limited training set." The model does not include inorganics so it should not be used for ingredients such as Copper Gluconate or ingredients containing silicon. As presented in the CIR reports, the model is a "black box" and does not identify the endpoint for which the NOAEL was estimated, nor does it indicate whether developmental and reproductive toxicity endpoints are considered. Although this tool may be useful for screening, it is not appropriate for predicting NOAELs for use in quantitative risk assessments in CIR reports.

Suggestions for Conducting a Quantitative Risk Assessment

We do not think that a quantitative systemic risk assessment needs to be completed for each CIR report. Quantitative systemic risk assessments should be completed on a case-by-case basis depending on the characteristics of the ingredient under review and the estimated exposure. When completed, a quantitative systemic risk assessment should be based on a specific endpoint of concern that has been identified for that ingredient and should be protective for other identified endpoints of concern, including developmental and reproductive toxicity and dermal irritation and sensitization.

For estimating exposure, we suggest that in addition to the SCCS Notes of Guidance for exposure parameters, other sources, such as the PCPC habits and practices data should also be used. The descriptions in the CIR report should clearly explain what the values used in the exposure assessment represent.

Exposure should be estimated for high exposure products, e.g., products intended to be used on a large surface area of the body, not just the products with the highest reported use concentrations. If the literature contains measurements of actual exposure, the measured values should be used rather than estimated values. We encourage CIR staff to continue to calculate exposure values clearly distinguishing between ingredient and product exposure, and

[1] Toropov AA, Toropova AP, Pizzo F, Lombardo A, Gadaleta D, Benfenati E. CORAL: model for no observed adverse effect level (NOAEL). Mol Divers. 2015;19:563-575.

[2] Selvestrel G, Robino F, Baderna D, et al. SpheraCosmolife: a new tool for the risk assessment of cosmetic products. ALTEX. 2021;38(4):565-579.

in addition to systemic exposure values, to calculate mg/cm^2 doses for those ingredients with evidence of dermal sensitization using methods developed by RIFM[3].

In conducting a quantitative risk assessment, the critical effect should be identified before a NOAEL is determined. Once a NOAEL has been determined, either through data or modeling, it is important to ask if it makes sense. For the Octoxynols, the modeled NOAELs do not seem to match the repeated dose data and the developmental and reproductive toxicity data that are presented in the report. For Copper Gluconate, ECHA identified a reproductive NOAEL of 318 mg/kg and a developmental NOAEL of 793 mg/kg. The systemic toxicity section of the CIR report indicates that ECHA used a QSAR approach to estimate a systemic LOAEL of 94.7 mg/kg. These values differ from the value of 1,687 mg/kg/day estimated by the CORAL NOAEL model. Without an explanation of why the values are so different, the credibility of the CIR report may be questioned.

In presenting NOAEL values in CIR reports, they should be stated only to 2 significant digits. The CIR report should also make it clear why an MoS of 100 is typically sufficient, i.e., assuming a default 10x interspecies and 10x intraspecies extrapolation factors, or factors to address duration of exposure differences.

Summary

We encourage CIR staff to continue to include transparent exposure assessments in CIR reports, both for systemic and dermal exposure. Based on data in the report, endpoint(s) of concern should be determined, and NOAELs (and LOAELs) identified. For those ingredients that lack toxicity at the tested doses, e.g., fatty acids, normal constituents of the body, that should be clearly stated. Models, such as the OECD toolbox are helpful for identifying structural alerts for skin sensitization and for use as part of a defined approach for skin sensitization (OECD Guideline 497) or for contributing to a weight of evidence approach. These models are not yet ready for the identification of a NO(A)EL for risk assessments. CIR SSC would be happy to review the use of new tools as applied to CIR assessments as they are being considered for use in a CIR report.

Margin of safety calculations should be calculated if an exposure assessment is completed, and a NO(A)EL (or LOAEL) is identified. A margin of safety calculation should not be considered essential for the completion of a CIR safety assessment.

[3] Api AM, Basketer D, Bridge J, et al. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Reg Tox and Pharm. 2020; 118 https://doi.org/10.1016/j.yrtph.2020.104805

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Jinqiu Zhu, PhD, DABT, ERT, DCST, CIR Toxicologist
Date: March 4, 2024
Subject: Strategy Memo on Applying Maximum Use Concentration in Exposure Estimate

In preparing a risk assessment for cosmetic ingredients, determining consumer exposure levels is essential for establishing the safety margin. Conservative estimates of external exposure might take into account the highest reported use concentration across different product categories. Although CIR reports feature a table that outlines the frequency and concentration of use of the ingredient across different product categories based on FDA's database, this information by itself does not directly reveal the levels of exposure. Under in-use exposure scenarios, assessing exposure involves more than just the concentration of use. For instance, the extent of skin exposure (skin surface area of application) and the retention rates (the proportion of the product that retained on the skin) vary greatly across different product categories. These variations can alter exposure patterns and the quantity of substances absorbed internally, thereby impacting the risk evaluation. The Panel, of course, is already aware of these details; however, it is proposed herein that these details could be fleshed out in report text, resulting in greater transparency and value to the readers. To assist the Panel in documenting the assessment of risk in their reports, the inclusion of a table of the calculated exposure amounts may be beneficial when relevant exposure parameters are available for a specific product category.

In the comments on the SLR of Copper Gluconate, the Council recommended that if the Panel would like MoS calculations included in the report, *the products for which the calculations are completed should be those resulting in the highest exposure, rather than the products with the highest concentration. For example, the highest use concentration for moisturizers was 0.0025%. Because moisturizers may be applied over the whole body and left on, they may result in higher exposure than baby shampoo and skin cleansing products*. The CIR Science & Support Committee (SSC) also commented that *exposure should be estimated for high exposure products, e.g., products intended to be used on a large surface area of the body, not just the products with the highest reported use concentrations* (*CIRSSC_risk_032024*, submitted to the Panel at the current meeting). To elucidate the difference between highest concentration and highest exposure in assessing consumer exposure, a comparative calculation is provided below. (Exposure parameters are retrieved from the SCCS Note of Guidance.[1])

i). Copper Gluconate at 0.1% in skin cleansing preparations (e.g., make-up remover)

Estimated daily amount applied make-up remover: 5 g/d = 5000 mg/d
Retention factor: 0.1
Type of exposure: rinse-off
Time of exposure: 0.5 h
Surface area involved: 565 cm^2
Relative daily exposure of make-up remover: 5000 mg/d × 0.1 (retention factor) = 500 mg/d
Exposure to Copper Gluconate as used in make-up remover: 500 mg/d × 0.1% (use concentration) = **0.5 mg/d**

ii). Copper Gluconate at 0.0025% in moisturizers (e.g., body lotion)

Estimated daily amount applied body lotion: 7.82 g/d = 7820 mg/d
Retention factor: 1.0
Type of exposure: leave-on
Time of exposure: 24 h

Surface area involved: 15,670 cm^2
Relative daily exposure of body lotion: 7820 mg/d × 1.0 (retention factor) = 7820 mg/d
Exposure to Copper Gluconate as used in body lotion: 7820 mg/d × 0.0025% (use concentration) = **0.1955 mg/d**

The calculated results indicate that daily exposure of Copper Gluconate resulting from the use of the make-up remover (0.5 mg/d) is relatively greater than that from the body lotion (0.1955 mg/d). Additionally, the exposure of Copper Gluconate from other product categories are summarized in Table 1. It should be noted that when a product category is not specified in a type of cosmetics exposure, the category with the highest exposure level for that exposure type has been selected for the estimate. For example, shower gel is selected to represent *skin cleansing* cosmetics since it can be applied on the entire body, comparing to other rinse-off cleaning products. Likewise, make-up remover is chosen to represent *other makeup preparations*, rather than lipsticks or eye makeup which are associated with smaller area of skin contact.

Table 1 Concentration of Use (2022)[2] and Exposure by FDA Product Category – Copper Gluconate

Product Category/Type of cosmetics exposure	Daily Exposure by Product Category* (mg/d)	Maximum Concentration of Use	Daily Exposure Based on the Highest Use Concentration (mg/d)	Note
Baby shampoos	19.6	0.2%	0.0392	Surface area for application a baby (3 years) is calculated to be 256 cm^2. #
Other baby products	3044	0.0005%	0.0152	Exposure amount of Baby body lotion applied. The total body surface area is 6100 cm^2 for a baby (3 years).[3]
Eyeliners	5	0.006%	0.0003	
Eye lotions	20	0.0005%	0.0001	Exposure amount of Eye shadow applied
Hair conditioners	40	0.000025%	0.00001	
Shampoos (noncoloring)	110	0.000025%	0.0000275	
Other makeup preparations	500	0.0025%	0.0125	Exposure amount of Make-up remover applied
Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	190	0.0023-0.1%	0.19	Exposure amount of Shower gel applied
Face and neck products Not spray	1540	0.0005-0.003%	0.0462	Exposure amount of Face cream/lotion applied
Moisturizing products Not spray	7820	0.0005-0.0025%	0.1955	Exposure amount of Body lotion applied
Night products Not spray	1540	0.005%	0.077	Exposure amount of Face cream/lotion used
Paste masks and mud packs	308 γ	0.0001-0.005%	0.0154	Exposure amount of Face mask applied
Other skin care preparations	2160	0.0005%	0.0108	Exposure amount of Hand cream applied
Other suntan preparations	--	0.0005%	--	Relevant data not available

***** Exposure parameters are retrieved from the SCCS NoG.[1]
# According to the dermal exposure factors from the U.S. Environmental Protection Agency for a baby (3 years old), the total body surface area is 6100 cm^2, with the head's surface area making up 8.4% of the total. It is assumed that half of the baby's head is exposed.[3] According to SCCS NoG, the application surface area for shampoo on an adult is 1440 cm^2, associated with a daily exposure of 110 mg.
γ Exposure amount is provided by Vermeer Cosmolife.[4]

Similarly, the exposures of BHA across different product categories/types of cosmetics are presented in Table 2. BHA is an authorized food additive in the EU with an acceptable daily intake (ADI) of 1.0 mg/kg bw/day established by European Food Safety Authority (EFSA) Panel on Food Additives and Nutrient Sources added to Food (ANS).[5] Hence, for an adult weighing 60 kg, the permissible daily intake limit is 60 mg (or 60,000 µg). The conservative exposure estimates provided in Table 2, which effectively *distinguish the exposure values between ingredient and product exposure* as recommended by the CIRSSC in their comments on risk assessment (*CIRSSC_risk_032024*), demonstrate that daily

cosmetic use leads to BHA exposure levels significantly below the ADI limit. In this case, performing a margin of safety (MoS) calculation might be unnecessary, since the risk can be evaluated based on the exposure assessment results.

Table 2 Concentration of Use (2023) [6] and Exposure by FDA Product Category – BHA

Product Category/Type of cosmetics exposure	Daily Exposure by Product Category* (mg/d)	Maximum Concentration of Use	Daily Exposure Based on the Highest Use Concentration (mg/d)	Note
Eyebrow pencils	20	0.05%	0.01	Exposure amount of Eye shadow applied
Eyeliners	5	0.05%	0.0025	
Eye shadows	20	0.000086-0.05%	0.01	
Mascaras	25	0.03%	0.0075	
Other fragrance preparations	1500 #	0.001%	0.015	Exposure amount of Eau de toilette spray applied
Hair conditioners	40	0.0084%	0.00336	
Hair sprays Aerosol	5000 γ	0.00000004%	0.000002	
Shampoos (noncoloring)	110	0.0024%	0.00264	
Face powders	85 †	0.05%	0.0425	
Foundations	510	0.02%	0.102	
Lipstick	60	0.05%	0.03	
Other manicuring preparations	300 #	0.15%	0.45	Exposure amount of nail polish applied
Dentifrices	138	0.00045%	0.000621	Exposure amount of toothpaste applied
Bath soaps and detergents	50 #	0.0006-0.0022%	0.0011	Exposure amount of bath oil, salts, etc. applied
Deodorants Not spray Aerosol	 1500 6540	 0.00076% 0.000051%	 0.0114 0.00334	
Skin cleansing (cold creams, cleansing lotions, liquids and pads)	190	0.00025%	0.000475	Exposure amount of shower gel applied
Face and neck products Not spray	1540	0.00013-0.013%	0.20	Exposure amount of face cream/lotion applied
Body and hand products Not spray	7820	0.0021%	0.164	Exposure amount of body lotion applied
Night products Not spray	308 #	0.00001%	0.000031	Exposure amount of face mask applied

* Exposure parameters are retrieved from the SCCS NoG[1]

Exposure amount is provided by Vermeer Cosmolife[4]

γ Exposure amount is provided by CTFA (currently known as PCPC) habits and practices data[7]

† Exposure amount is provided by Steiling et al. 2018[8]

Of note, BHA is reported to be used at concentrations up to 1% for *other nail products* and 5 mg/g for *mascara/eyelash products* in California Safe Cosmetics Program (CSCP) Product Database.[9]

In summary, a thorough and conservative exposure assessment requires evaluating the highest exposure levels across various product categories by taking into account all relevant exposure parameters, including the maximum usage concentration. The necessary exposure parameters for each category of products can be retrieved from various data sources as needed, such as SCCS NoG[1], PCPC habits and practices data[7], EPA exposure factors handbook[3], RIFM exposure models[10], and other relevant peer-reviewed articles[8].

The Panel is being asked to consider the utility of including a table that features exposure estimates across various product categories in CIR reports, particularly focusing on external exposure for dermal uptake. If deemed useful, the Panel is requested to also decide on the preferred product type to use in cases where specific information on cosmetics exposure is lacking (for instance, is it appropriate to use *shower gel* as a representative for *skin cleansing products*; can *face mask* reasonably represent *night products (not-spray)*; or is *baby body lotion* suitable to represent *other baby products*?)

References:

1. Scientific Committee on Consumer Safety (SCCS). *The SCCS's notes of guidance for the testing of cosmetic ingredients and their safety evaluation (12th Revision).* 2023. SCCS/1647/22.
2. Personal Care Products Council. Concentration of Use by FDA Product Category: Copper Gluconate. In: Unpublished data submitted by Personal Care Products Council on July 06, 2022; 2022.
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