ADMIN

CIR SSC Submission on Dermal Dosing in HRIPT Versus Product Use

EXPERT PANEL MEETING
September 11-12, 2023

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: August 18, 2023
Subject: CIR SSC submission on dermal dosing in HRIPT versus product use

The CIR Science and Support Committee (SSC) of the Personal Care Products Council submitted a Comparison of Ingredient Concentrations Tested in HRIPTs to Product Usage, dated July 11, 2023 (identified as *CIRSSC_DermalDosingHRIPT_092023*). Correspondingly, Dr. Donald Bjerke, Procter & Gamble, Chair of the CIR SSC, will be presenting to the Panel on the morning of the first day of the meeting (September 11) on this subject.

In their submission, the CIR SSC presents a comparison between a participant's exposure to cosmetic ingredients in an HRIPT and the anticipated exposure that arises from the use of individual cosmetic products. The concentration of use information and the HRIPT testing data, as featured in the CIR report on phytosteryl glutamates, serve as an exemplary illustration. The CIR SSC illustrates through a specific example that conducting an HRIPT at the maximum reported product use concentration is not always necessary if the dose per unit area in an HRIPT of another tested product meets or exceeds the dose per unit area following consumer exposure.

As discussed in the review paper referenced by the CIR SSC (ref. 3, McNamee et al. 2008), test material concentration (dose/unit area) is one of the vital factors considered in the conduct and interpretation of an HRIPT:

> *The concentration used is expressed as a dose/unit area of skin as defined by the **absolute amount** of test material applied and the area of skin exposed. …*
> *The selection of an appropriate concentration is crucial to avoid false negative results or the unnecessary induction of skin sensitization.*

Consequently, under certain circumstances, the confirmatory nature of HRIPT testing, rather than a focus on hazard identification, may need to be taken into account.

Upon consideration of the case example highlighted in the attached submission, what is the opinion of the Panel? Is an HRIPT at the maximum reported product use concentration always needed if the dose per unit area in an HRIPT of another tested product is greater than or equal to the dose per unit area following consumer exposure?

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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: July 11, 2023

SUBJECT: Comparison of Ingredient Concentrations Tested in HRIPTs to Product Usage

The CIR Science and Support Committee (CIR SSC) appreciates the opportunity to provide a comparison of a participant's exposure to cosmetic ingredients (mg/cm^2) in a human repeat insult patch test (HRIPT) compared to an individual's expected exposure (mg/cm^2) resulting from cosmetic product use. Information from the CIR report on phytosteryl glutamates will be used as an example.

The amount of cosmetic ingredient (mg) per skin surface area (cm^2) is the most important dose metric for skin sensitization. This is based on both human and animal data and several references to support this position are summarized in section 1.4.1 Dose metric in Api et al. (2008).[1]

In addition to three negative guinea pig maximization tests, the CIR report on phytosteryl glutamates includes two negative HRIPTs on products containing Phytosteryl/Behenyl/Octyldodecy Lauroyl Glutamate. The concentrations tested were 5% in one HRIPT, and 5.99% in the second. In both tests, 0.2 ml of the test material was applied to a 4 cm^2 patch under occlusive conditions. The dose under occlusive patch per unit area in the study of the 5.99% product is approximately 2.995 mg Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate per cm^2 skin.

The table below compares the HRIPT study exposure (2.995 mg/cm^2) to maximum reported use levels included in the CIR report on phytosteryl glutamates for several product categories and provides the margin of exposure (MoE; HRIPT study dose metric divided by product maximum exposure dose metric). An MoE of 1 or greater is considered acceptable. The cosmetic exposure data are based on 90 to 95th percentile exposures from published habits and practices data that are summarized in Table 3 of Api et al., 2008. It shows that the HRIPT for the product containing 5.99% Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate tested under occlusive

[1] Api AM, Basketer DA, Caby PA, et al. 2008. Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. *Regulatory Toxicology and Pharmacology* 52: 2-23.
https://fragrancematerialsafetyresource.elsevier.com/sites/default/files/FA-1-Api-Research.pdf

conditions are sufficient to cover the dose/unit area of skin for all the maximum reported usage scenarios included in the CIR report, including uses up to 25% in lipstick and rouges. This example shows that a confirmatory HRIPT at the maximum reported use concentration is not always necessary.

Product type	**Exposure to product (reference)**	**Maximum % of phytosteryl glutamate in product**	**Exposure to phytosteryl glutamate from product**	**Margin of exposure compared to HRIPT***
Lipstick	11.46 mg/cm^2 (Api et al., 2008[1])	25%	2.865 mg/cm^2	1.04
Rouges	4.2 mg/cm^2 (IFRA RIFM QRA 2015[2])	25%	1.05 mg/cm^2	2.9
Eye shadows	2.17 mg/cm^2 (Api et al., 2008[1])	9%	0.189 mg/cm^2	15.8
Face and neck products	2.70 mg/cm^2 (Api et al., 2008[1])	8%	0.216 mg/cm^2	13.9
Hand and body lotions	1.12 mg/cm^2 (Api et al., 2008[1])	1%	0.0112 mg/cm^2	267

*HRIPT study exposure 2.995 mg/cm^2/exposure to ingredient from product

We continue to support a weight of the evidence approach that examines all the sensitization data when making a determination of safety. Regarding confirmatory HRIPT testing, an HRIPT at the maximum reported product use concentration is not always needed if the dose per unit area in an HRIPT of another tested product is greater than or equal to the dose per unit area following consumer exposure. Consumer product exposure data typically uses 95th percentile exposure, and HRIPTs are often conducted under occlusive patch conditions (to enhance dermal penetration). A helpful review of critical factors in the conduct and interpretation of the HRIPT has been published.[3]

[2] IFRA RIFM QRA Information Booklet version 7.1 July 2015 (category 5) https://ifrafragrance.org/docs/default-source/ifra-code-of-practice-and-standards/background-scientific-information-and-guidelines/ifra-rifm-qra-information-booklet-v7-1.pdf?sfvrsn=1426bcb8_0

[3] McNamee PM, Api AM, Basketter DM, et al. 2008. A review of critical factors in the conduct and interpretation of the human repeat insult patch test. *Regulatory Toxicology and Pharmacology* 52: 24-34.