Data Supplement

Caprylhydroxamic Acid

Coconut

Glycerin Ethoxylates

Honey

MCI-MI

Pomegranate

CIR EXPERT PANEL MEETING DECEMBER 9-10, 2019

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume MMF
Senior Director
Date: December 2, 2019
Subject: Caprylhydroxamic Acid – Wave 2

Attached is an email (*caphyd122019wave2_ status update*) that was received from the company that has commissioned a human repeated insult patch test (HRIPT) and accompanying quantitative risk assessment (QRA) on Caprylhydroxamic Acid, in response to the IDA that was issued at the June 2019 Panel meeting. According to the email, the HRIPT was initiated, but the results and the QRA will not be available in time for the December meeting.

The company does anticipate submitting the information in time for the March 2020 Expert Panel meeting, and is requesting that the Panel table consideration of the report on Caprylhydroxamic Acid until that meeting. As indicated in my original transmittal memo to the Panel for this report (dated November 15), the Panel has the option to table this review until the data are received. If this option is chosen, the Panel is asked to set a schedule for when the report will return for their consideration. Alternatively, the Panel can formulate a tentative conclusion and issue a Tentative Report for public comment, and if appropriate, re-evaluate the conclusion when the requested data are received.

From: Fevola, Mike
To: Bart Heldreth; Monice Fiume
Subject: HRIPT and QRA status update
Date: Monday, December 2, 2019 8:07:47 AM
Importance: High

Dear Bart and Monice:

As you are already aware, in response to the CIR Expert Panel's finding of Insufficient Data for Caprylhydroxamic Acid issued at the June 2019 meeting of the Expert Panel, INOLEX commissioned the additional human repeat insult patch testing (HRIPT) and associated quantitative risk assessment (QRA) requested by the Panel. To aid in design of the HRIPT study, data analysis, and completion of the QRA, INOLEX identified and engaged an independent consultant for subject matter expertise on clinical testing for skin sensitization and determination of no expected sensitization induction limit (NESIL) values.

The HRIPT protocol was approved and initiated in Oct 2020. INOLEX intends to submit HRIPT results upon receipt of a final clinical study report from the study site. A full QRA report based on the NESIL value obtained from the HRIPT will also be submitted at that time. Regretfully, completion of the HRIPT and QRA reports will not occur in time for the Dec 2019 Expert Panel meeting. Submission is anticipated to be no later than 1 Feb 2020.

It is the recommendation of INOLEX that the report for Caprylhydroxamic Acid be tabled until the March 2020 meeting of the Expert Panel so that the results of the HRIPT and the QRA can be taken into account when a conclusion is determined. We politely request that CIR support this recommendation and encourage the Expert Panel to table the CHA report until March.

Please feel free to contact me with any questions or concerns regarding this matter. Thank you.

Sincerely,
Mike

Michael J. Fevola PhD | vice president, research & development

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: December 2, 2019
Subject: Draft Safety Assessment on *Cocos nucifera* (Coconut)-Derived Ingredients – Wave 2

Enclosed are the summaries of two human repeat insult patch tests (HRIPTs). In the first study, a rinse-off product containing 0.3% Cocos Nucifera (Coconut) Fruit, diluted to 1% in tap water (effective test concentration, 0.003% Cocos Nucifera (Coconut) Fruit), produced low level reactions in 7 out of 110 subjects during induction and 6 out of 110 subjects during challenge. The study authors concluded that this product was not sensitizing. In the second study, a leave-on product containing 0.098% Cocos Nucifera (Coconut) Fruit Juice (tested as is) was not irritating or sensitizing to 107 subjects.

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Memorandum

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

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

DATE: November 19, 2019

SUBJECT: Cocos Nucifera (Coconut) Fruit and Cocos Nucifera (Coconut) Fruit Juice

Anonymous. 2019. Summary of an HRIPT of a Product Containing 0.3% Cocos Nucifera (Coconut) Fruit.

Anonymous. 2019. Summary of an HRIPT of a Product Containing 0.098% Cocos Nucifera (Coconut) Fruit Juice.

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Nov 2019

Product Number	% Cocos Nucifera (Coconut) Fruit	Product Type	HRIPT Test Yes/No	Occlusivity	Completed Subjects	Did formula induce an allergic response	Number of Subjects Exhibiting Low Level Reaction During Induction	Number of Subjects Exhibiting High Level Reaction During Induction	Number of Subjects Exhibiting Low Level Reaction During Challenge	Number of Subjects Exhibiting High Level Reaction During Challenge	pass/fail	comments
1	0.3	RINSE OFF	YES	OCCLUSIVE	110	NO	7	0	6	0	PASS	Did not induce Dermal Sensitization in any of the subjects tested.

Product 1

ICDRG Reading Scale	Degree
No Visible Reaction	0
Faint, Minimal Erythema	±
Erythema	1
Intense Erythema, Induration	2
Intense Erythema, Induration, Vesicles	3
Severe reaction with erythema, induration, Vesicles, Pustules (May be weeping)	4
Edema	E

Details of Test Methodology and Results	
0	panelist discontinued due to reactions
24 hrs, 48 hrs	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge Patch
24 hrs, 48 hrs, 72 hrs, 96 hrs	challenge readings
0.2 gm	Amount of product applied
Test Material Concentration/Dilution	1% in tap water

Grading Scale Interpretation	
Low Level Reactions	0 or 1
High Level Reaction	2 and above

Nov 2019

Product Number	% Cocos Nucifera (Coconut) Fruit Juice	Product Type	HRIPT Test Yes/No	Occlusivity	Completed Subjects	Did formula induce an allergic response	Number of Subjects Exhibiting Low Level Reaction During Induction	Number of Subjects Exhibiting High Level Reaction During Induction	Number of Subjects Exhibiting Low Level Reaction During Challenge	Number of Subjects Exhibiting High Level Reaction During Challenge	pass/fail	comments
1	0.098	LEAVE ON	YES	OCCLUSIVE	107	NO	0	0	1	0	PASS	Did not induce significant deraml irritation nor any evidence of dermal sensitization in any of the human subjects tested.

Product 1

ICDRG Reading Scale	Degree
No Visible Reaction	0
Faint, Minimal Erythema	±
Erythema	1
Intense Erythema, Induration	2
Intense Erythema, Induration, Vesicles	3
Severe reaction with erythema, induration, Vesicles, Pustules (May be weeping)	4
Edema	E

Details of Test Methodology and Results	
0	panelist discontinued due to reactions
24 hrs	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge Patch
24 hrs, 48 hrs, 72 hrs, 96hrs	challenge readings
0.2 gm	Amount of product applied
Test Material Concentration/Dilution	As Is/Neat

Grading Scale Interpretation	
Low Level Reactions	0 or 1
High Level Reaction	2 and above

Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Preethi Raj
Senior Scientific Writer/Analyst
Date: December 2, 2019
Subject: Wave 2 Data on Glycerin Ethoxylates

Four human repeated insult patch test (HRIPT) summaries (two on Glycereth-7 and two on Glycereth-26) were received from the Council (*glyeth122019wave2_data1*), and are summarized below. Original data files (*glyeth122019wave2_data2, glyeth122019wave2_data3*) have also been attached for legibility.

A leave-on product containing 1% Glycereth-7 was tested in an HRIPT in 199 subjects (*glyeth122019wave2_data2*).[1] The test material was applied occlusively for 24 to 48 h via 9 applications made over a 3-week induction period. After a 2-week rest period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications, and reactions were scored 24, 48, 72, and 96 h after application. Four subjects exhibited low-level reactions (0 - 1 score, on a 0 - 4 scale) during induction; no other responses were noted during induction, or during challenge. The researchers concluded that the test material did not induce dermal sensitization.

A rinse-off product containing 2% Glycereth-7 was tested in a similar occlusive HRIPT in 211 subjects (*glyeth122019wave2_data2*).[1] The test material was diluted to 1% v/v tap water (effective test concentration, 0.02%). Two subjects exhibited low-level reactions during induction, and 11 subjects exhibited low-level reactions during challenge. The researchers concluded that although there was no primary dermal irritation potential, cumulative dermal irritation and sensitization potential were observed.

A rinse-off product containing 3% Glycereth-26 was tested as received in a semi-occlusive HRIPT in 103 subjects (*glyeth122019wave2_data3*).[2] One participant withdrew due to an adverse reaction; 4 subjects exhibited low-level reactions during induction, and 1 subject exhibited a low-level reaction during challenge. The researchers concluded that although there was no primary dermal irritation, cumulative dermal irritation and sensitization potential was observed.

A leave-on product containing 3% Glycereth-26 was tested as received in an occlusive HRIPT in 208 subjects (*glyeth122019wave2_data3*).[2] No participants withdrew due to adverse reactions; 38 subjects exhibited low-level reactions during induction, no subjects exhibited any reactions during challenge. The researchers concluded that the test material did not induce dermal sensitization.

1. Anonymous. 2019. Summaries of Two HRIPTs (one product containing 2% Glycereth-7, one product containing 1% Glycereth-7). (Unpublished data submitted by Personal Care Products Council on November 19, 2019.)

2. Anonymous. 2019. Summaries of Two HRIPTs (both products contain 3% Glycereth-26). (Unpublished data submitted by Personal Care Products Council on November 19, 2019.)

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Memorandum

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

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

DATE: November 19, 2019

SUBJECT: Glycereth-7 and Glycereth-26

Anonymous. 2019. Summaries of Two HRIPTs (one product containing 2% Glycereth-7, one product containing 1% Glycereth-7).

Anonymous. 2019. Summaries of Two HRIPTs (both products contain 3% Glycereth-26).

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Nov. 2019

Product Number	% Glycereth-7	Product Type	HRIPT Test Yes/No	Occlusivity	Completed Subjects	Did formula induce an allergic response	Number of Subjects Exhibiting Low Level Reaction During Induction	Number of Subjects Exhibiting High Level Reaction During Induction	Number of Subjects Exhibiting Low Level Reaction During Challenge	Number of Subjects Exhibiting High Level Reaction During Challenge	pass/fail	comments
1	2	RINSE OFF	YES	OCCLUSIVE	211	NO	2	0	11	0	PASS	There was no primary dermic irritation potential, cumulative dermic irritation potential and sensitization potential observed.
2	1	LEAVE ON	YES	OCCLUSIVE	199	NO	4	0	0	0	PASS	Did not induce dermal sensitization in any of the human subjects tested.

Product 1

ICDRG Reading Scale	Response
No visible reaction	0
Faint, minimal erythema	±
Erythema	1
Intense erythema, induration	2
Intense erythema, induration, vesicles	3
Severe reaction with erythema, induration, vesicles, pustules (may be weeping)	4
Edema	E

Details of Test Methodology and Results	
0	panelist discontinued due to reactions
24 hrs, 48 hrs,	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge Patch
24 hrs, 48 hrs, 72hrs, 96 hrs	challenge readings
0.2 gm	Amount of product applied
Occlusive	Patch type
Test Material Concentration/Dilution	1% v/v in tap water

Grading Scale Interpretation	
Low Level Reactions	0 or 1
High Level Reaction	2 and above

Product 2

ICDRG Reading Scale	Degree
No visible reaction	0
Faint, minimal erythema	±
Erythema	1
Intense erythema, induration	2
Intense erythema, induration, vesicles	3
Severe reaction with erythema, induration, vesicles, pustules (may be weeping)	4
Edema	E

Details of Test Methodology and Results	
0	panelist discontinued due to reactions
24 hrs, 48 hrs,	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge Patch
24 hrs, 48 hrs, 72hrs, 96 hrs	challenge readings
0.2 gm	Amount of product applied
Occlusive	Patch Type
Test Material Concentration/Dilution	As is/Neat

Grading Scale Interpretation	
Low Level Reactions	0 or 1
High Level Reaction	2 and above

Nov 2019

Product Number	% Glycereth-26	Product Type	HRIPT Test Yes/No	Occlusivity	Completed Subjects	Did formula induce an allergic response	Number of Subjects Exhibiting Low Level Reaction During Induction	Number of Subjects Exhibiting High Level Reaction During Induction	Number of Subjects Exhibiting Low Level Reaction During Challenge	Number of Subjects Exhibiting High Level Reaction During Challenge	pass/fail	comments
1	3	RINSE OFF	YES	SEMI-OCCLUSIVE	103	NO	4	0	1	0	PASS	There was no primary dermic irritation potential; cumulative dermic irritation potential and sensitization potential observed.
2	3	LEAVE ON	YES	OCCLUSIVE	208	NO	38	0	0	0	PASS	Did not induce dermal sensitization in any of the human subjects tested.

Product 1

ICDRG Reading Scale	Response	
No Reaction	Negative (-)	
Minimal or doubtful response, slightly different from surrounding normal skin	Dubious (?)	
Definite erythema, no edema	Positive (+)	
Definite erythema, definite edema	Positive (++)	
Definite erythema, definite edema and vesiculation	Positive (+++)	

Details of Test Methodology and Results	
1	panelist discontinued due to reactions
24 hrs, 48 hrs,	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge Patch
48 hrs, 72 hrs	challenge readings
0.02 ml	Amount of product applied
Test Material Concentration/Dilution	Neat

Grading Scale Interpretation	
Low Level Reactions	0 or 1
High Level Reaction	2 and above

Product 2

Induction Grading Scale		Challenge Grading Scale	
ICDRG Reading Scale	Degree	ICDRG Reading Scale	Degree
No evidence of irritation	0	No visible erythema	0
Minumal erythema, barely perceptible	1	Mild erythema(faint pink to definite pink)	1
Definite erythema, readily visible; or minimal edema; or minimal papular response	2	Moderate erythema (definite redness)	2
Erythema and papules	3	Severe erythema (very intense redness)	3
Definite edema	4		
Erythema, edema, and papules	5		
Vesicular eruption	6		
Strong reaction spreading beyond test site	7		

Details of Test Methodology and Results	
0	panelist discontinued due to reactions
24 hrs, 48 hrs,	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge Patch
48 hrs, 96 hrs	challenge readings
20 µl	Amount of product applied
Test Material Concentration/Dilution	As is/Neat

Grading Scale Interpretation	
Low Level Reactions	0 or 1
High Level Reaction	2 and above

Product Number	% Glycereth-7	Product Type	HRIPT Test Yes/No	Occlusivity	Completed Subjects	Did formula induce an allergic response	Number of Subjects Exhibiting Low Level Reaction During Induction	Number of Subjects Exhibiting High Level Reaction During Induction	Number of Subjects Exhibiting Low Level Reaction During Challenge	Number of Subjects Exhibiting High Level Reaction During Challenge	pass/fail	comments
1	2	RINSE OFF	YES	OCCLUSIVE	211	NO	2	0	11	0	PASS	There was no primary dermic irritation potential; cumulative dermic irritation potential and sensitization potential observed.
2	1	LEAVE ON	YES	OCCLUSIVE	199	NO	4	0	0	0	PASS	Did not induce dermal sensitization in any of the human subjects tested.

Product 1

ICDRG Reading Scale	Response
No visible reaction	0
Faint, minimal erythema	±
Erythema	1
Intense erythema, induration	2
Intense erythema, induration, vesicles	3
Severe reaction with erythema, induration, vesicles, pustules (may be weeping)	4
Edema	E

Details of Test Methodology and Results	
0	panelist discontinued due to reactions
24 hrs, 48 hrs,	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge Patch
24 hrs, 48 hrs, 72hrs, 96 hrs	challenge readings
0.2 gm	Amount of product applied
Occlusive	Patch type
Test Material Concentration/Dilution	1% v/v in tap water

Grading Scale interpretation	
Low Level Reactions	0 or 1
High Level Reaction	2 and above

Product 2

ICDRG Reading Scale	Degree		
No visible reaction	0		
Faint, minimal erythema	±		
Erythema	1		
Intense erythema, induration	2		
Intense erythema, induration, vesicles	3		
Severe reaction with erythema, induration, vesicles, pustules (may be weeping)	4		
Edema	E		

Details of Test Methodology and Results	
0	panelist discontinued due to reactions
24 hrs, 48 hrs,	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge Patch
24 hrs, 48 hrs, 72hrs, 96 hrs	challenge readings
0.2 gm	Amount of product applied
Occlusive	Patch Type
Test Material Concentration/Dilution	As Is/Neat

Grading Scale interpretation	
Low Level Reactions	0 or 1
High Level Reaction	2 and above

Product Number	% Glycereth-26	Product Type	HRIPT Test Yes/No	Occlusivity	Completed Subjects	Did formula induce an allergic response	Number of Subjects Exhibiting Low Level Reaction During Induction	Number of Subjects Exhibiting High Level Reaction During Induction	Number of Subjects Exhibiting Low Level Reaction During Challenge	Number of Subjects Exhibiting High Level Reaction During Challenge	pass/fail	comments
1	3	RINSE OFF	YES	SEMI-OCCLUSIVE	103	NO	4	0	1	0	PASS	There was no primary dermic irritation potential; cumulative dermic irritation potential and sensitization potential observed.
2	3	LEAVE ON	YES	OCCLUSIVE	208	NO	38	0	0	0	PASS	Did not induce dermal sensitization in any of the human subjects tested.

Product 1

ICDRG Reading Scale	Response	
No Reaction	Negative (-)	
Minimal or doubtful response, slightly different from surrounding normal skin	Dubious (?)	
Definite erythema, no edema	Positive (+)	
Definite erythema, definite edema	Positive (++)	
Definite erythema, definite edema and vesiculation	Positive (+++)	

Details of Test Methodology and Results	
1	panelist discontinued due to reactions
24 hrs, 48 hrs,	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge Patch
48 hrs, 72 hrs	challenge readings
0.02 ml	Amount of product applied
Test Material Concentration/Dilution	Neat

Grading Scale interpretation	
Low Level Reactions	0 or 1
High Level Reaction	2 and above

Product 2

Induction Grading Scale		Challenge Grading Scale	
ICDRG Reading Scale	**Degree**	**ICDRG Reading Scale**	**Degree**
No evidence of irritation	0	No visible erythema	**0**
Minimal erythema, barely perceptible	1	Mild erythema(faint pink to definite pink)	1
Definite erythema, readily visible; or minimal edema; or minimal papular response	2	Moderate erythema (definite redness)	2
Erythema and papules	3	Severe erythema (very intense redness)	3
Definite edema	4		
Erythema, edema, and papules	5		
Vesicular eruption	6		
Strong reaction spreading beyond test site	7		

Details of Test Methodology and Results	
0	panelist discontinued due to reactions
24 hrs, 48 hrs,	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge Patch
48 hrs, 96 hrs	challenge readings
20 µl	Amount of product applied
Test Material Concentration/Dilution	As Is/Neat

Grading Scale interpretation	
Low Level Reactions	0 or 1
High Level Reaction	2 and above

Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Priya Cherian
Scientific Writer/Analyst
Date: December 2, 2019
Subject: Wave 2 Data on Honey Extract

A summary of a human repeated insult patch test (HRIPT) on a rinse-off product containing 0.01% Honey Extract, that was received from the Council, is summarized below and attached (*honey122019wave2_data1*) for the Panel's review.

An HRIPT involving a product containing 0.01% Honey Extract was performed using 116 subjects.[1] The product was tested at a 1% dilution in water (effective test concentration, 0.0001% Honey Extract). During induction, the test substance was applied in an amount of 0.2 g, under an occlusive patch, for 24 - 48 h. This procedure was repeated for a total of 9 induction applications. The 9th application was followed by a 2-wk rest period, after which, the challenge phase was initiated. Reactions to challenge patches were scored at 24 h, 48 h, 72 h, and 96 h after patch application. Seven individuals displayed low-level reactions (mild erythema) during the induction phase, and one individual displayed a high-level reaction in the induction phase. Eight individuals displayed low-level reactions during the challenge phase. The test substance was considered by the researchers to be non-sensitizing.

1. Anonymous. 2019. Summary of an HRIPT (product contains 0.01% Honey Extract). (Unpublished data submitted by Personal Care Products Council on November 19, 2019.)

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Memorandum

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

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

DATE: November 19, 2019

SUBJECT: Honey Extract

Anonymous. 2019. Summary of an HRIPT (product contains 0.01% Honey Extract).

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Nov 2019

Product Number	% Honey Extract	Product Type	HRIPT Test Yes/No	Occlusivity	Completed Subjects	Did formula induce an allergic response	Number of Subjects Exhibiting Low Level Reaction During Induction	Number of Subjects Exhibiting High Level Reaction During Induction	Number of Subjects Exhibiting Low Level Reaction During Challenge	Number of Subjects Exhibiting High Level Reaction During Challenge	pass/fail	comments
1	0.01	RINSE OFF	YES	OCCLUSIVE	116	NO	7	1	8	0	PASS	Did not induce dermal Sensitization.

Product 1

ICDRG Reading Scale	Response
No visible reaction	0
Faint, minimal erythema	±
Erythema	1
Intense erythema, induration	2
Intense erythema, induration, vesicles	3
Severe reaction with erythema, induration, vesicles, pustules (may be weeping)	4
Edema	E

Details of Test Methodology and Results	
0	panelist discontinued due to reactions
24 hrs, 48 hrs,	patch duration
9	induction patches
3	weeks induction
2	week rest period
virgin site	challenge Patch
24 hrs, 48 hrs, 72 hrs, 96 hrs	challenge readings
0.2 gm	Amount of product applied
Test Material Concentration/Dilution	1% in tap water

Grading Scale Interpretation	
Low Level Reactions	0 or 1
High Level Reaction	2 and above

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: December 2, 2019
Subject: Draft Final Amended Safety Assessment on Methylchloroisothiazolinone and Methylisothiazolinone – Wave 2

Enclosed is a summary of a 13-week inhalation study of 14% MCI/MI in rats that follows OECD TG 413 (*mcimi122019wave2_data*). MCI/MI was tested at up to 2.64 mg active ingredient/m^3. The maximum NOEL was 0.34 mg/m^3.

CIR has also received comments from Women's Voices for the Earth within the 60-day comment period. These comments have been added to this Wave 2 package (*mcimi122019wave2_wvecomments*).

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November 21, 2019

13-Week Inhalation Toxicity Study in Rats (1984)

Study Summary

Four groups of 16 Crl:CD(SD)BR rats per sex per dose were exposed whole body for 6 hours per day, 5 days per week, for 13 weeks to 14% 5-chloro-2-methyl-4-isothiazolin-3-one/2-methyl-4-isothiazolin-3-one (11% CMIT/3% MIT) aerosol concentrations of 0.0, 0.34, 1.15, or 2.64 mg active ingredient (a.i.)/m^3. The test formulation aerosol particle size ranged from a mean mass median diameter of 1.1 to 1.4 µm and a geometric standard deviation of 1.9 to 2.0. Signs of intoxication, body weight, and ophthalmologic evaluations were conducted during the 13 week exposure period. Hematology, clinical chemistry, gross pathology, and histopathologic evaluations were conducted at study termination. No statistically or biologically significant effects were observed in the hematology, gross pathology, or ophthalmologic evaluations at any exposure level. Rats exposed to 2.64 mg/ m^3 exhibited signs resulting from exposure consistent with those produced by a sensory irritant (chromorhinorrhea, rhinorrhea, eye squint, bradypnea, and dyspnea). Decreased body weight gains, decreased male spleen weights, and decreased serum protein in females also occurred in rats exposed to 2.64 mg/ m^3. No treatment-related signs of intoxication, body weight effects, or organ weight effects were observed in the 0.34 or 1.15 mg/ m^3 groups. Treatment-related histopathologic findings consisting of slight to moderate incidences of eosinophilic droplets in the anterior respiratory mucosa of the nasal turbinates and slight rhinitis in the lining of the anterior portion of the nasal cavity were observed in the 2.64 mg/ m^3 treated animals. The only treatment-related histopathologic effect observed in the 1.15 mg/ m^3 animals was rhinitis of the nasal cavity. No treatment-related histopathologic effects were observed in the 0.34 mg/ m^3 group. All the histopathologic changes were very minor, potentially reversible, and generally reflective of minimal tissue responses to a very mild, low-grade respiratory irritant. On the basis of the occurrence of rhinitis, the most sensitive indicator of exposure in this study, the minimum observed effect level was 1.15 mg/ m^3 a.i. The maximum no observed effect level was 0.34 mg/ m^3 a.i.

GLP: Yes

Guideline: equivalent to OECD 413

WOMEN'S VOICES FOR THE EARTH
OUR HEALTH. OUR FUTURE. TOXIC FREE.

November 25, 2019

To the CIR:

I am writing to submit comments on the Amended Safety Assessment of Methylchloroisothiazolinone and Methylisothiazolinone to be discussed at the December 2019 meeting.

My comments include concerns over two specific issues:

1) The CIR SSC's QRA for these ingredients is not fully transparent in the Safety Assessment and should be clarified and amended, and it appears that there are errors in Table 3 which reports results of the QRA.

2) The current discussion of dermal sensitization rates of Methylchloroisothiazolinone and Methylisothiazolinone and the contribution of cosmetic product exposure to these rates is highly problematic in that it vastly underplays the recent epidemic of the problem globally, and discounts the responsibility (and ability) of the CIR to play a major role to advance public health.

1) CIR SSC's QRA for Methylchloroisothiazolinone and Methylisothiazolinone

There is one highly questionable data point presented in Table 3 which is that the highest reported maximum concentration of use in bubble baths is "0.000019 ppm". This very much appears to be an error. I have never seen any manufacturer report the presence of an intentional ingredient at such an incredibly low concentration - especially for a preservative, in which, quite obviously, this concentration would have no antibacterial efficacy whatsoever. This concentration is far below what even industry would consider a deminimus amount for any ingredient, there is no question in my mind that this number was reported in error. I believe that it is much more likely that the company reporting this concentration was reporting the actual concentration in the product, that is .000019 of the product which is equivalent to 19 ppm. And if this is the case, clearly the resulting margin of safety for bubble baths would be quite different and likely of concern. Given also that bubble bath products are predominantly used by children, and that the VCRP reports over 100 bubble bath products containing MCI/MI it would be prudent for the CIR to request and verify concentration information from bubble bath manufacturers to be better understand the actual exposure and potential risk from this product category.

Secondly, the discussion of the QRA in the safety Assessment is confusing as the text states:

> "*When using the exposure assumptions in this risk assessment on all reported VCRP product categories of use with the maximum concentrations of use, as set by the original CIR conclusion, of 7.5 ppm in leave-on products and 15 ppm in rinse-off products, an adequate MOS could not be assured for baby shampoo (MOS = 0.92), permanent wave (MOS =0.13), hair tints (MOS = 0.56), skin cleansing products (0.61), or cologne and toilet waters (0.50). Table 3 summarizes the QRA results.*"

However, Table 3 does not in fact include these MOS numbers for baby shampoo, permanent waves, hair tints, skin cleansing products or colognes and toilet waters. In the original QRA submitted in May by the SSC, there are three tables included (Table 5, Table 6 and Table 7) which display the various MOS's calculated. The numbers mentioned above in the text come from the original Table 6, but Table 3 of this Safety Assessment only report the results found in the original Table 5. It might be helpful to either include the full QRA in the Safety Assessment - or at least include all three tables (Table 5, 6 and 7) to explain where inadequate MOS's were calculated.

Having full information on how the QRA was done, and the full results that were calculated should be important information to manufacturers who are being required to complete a QRA to assess the appropriate applicable level for their product.

2) **The MCI/MI contact allergy epidemic**

There is some very important contextual information missing from the MCI/MI Safety Assessment– which is that the consensus of dermatological experts around the world is that there has been an **epidemic** of sensitizations to MI and MCI/MI caused by the significant increases in the use of these chemicals in cosmetics in recent decades. The rate and speed at which MI and MCI/MI became known as significant skin sensitizers was unprecedented and caused alarm internationally. Importantly, this epidemic has largely occurred in the time since the CIR last reviewed these chemicals. This aspect is not currently mentioned in this safety assessment which appears to be a major oversight. Unlike how they are portrayed in the current draft, isothiazilinones are not just run of the mill sensitizers, but have caused an unprecedented significant epidemic of morbidity specifically due to their use in cosmetics. It is highly relevant to relay these facts in this safety assessment.

Quotes from recent papers:

"*Preservative sensitivity patterns evolve with changing use patterns in products. During the last decade, the use of methylisothiazolinone (MI) at higher concentrations in both leave-on and rinse-off products has significantly increased…The epidemic of isothiazolinone sensitivity documented in Europe is now in North America."*

Zirwas, M. J., Hamann, D., Warshaw, E. M., Maibach, H. I., Taylor, J. S., Sasseville, D., … Belsito, D. V. (2017). **Epidemic of Isothiazolinone Allergy in North America**. *Dermatitis*, *28*(3), 204-209. doi:10.1097/der.0000000000000288

"Methylisothiazolinone (MI) is a preservative commonly used in water-based personal care products. Increases in the allowable concentration of MI alone in these products has led to an epidemic of allergic contact dermatitis (ACD)…personal care products are the most common source of MI contact allergy"

Reeder M. Atwater AR. (2019) **Methylisothiazolinone and isothiazolinone allergy**. Cutis. Aug 2019, 104(2): 94-96.

"*The prevalence of MI and MCI/MI contact allergy increased significantly from 2010 to 2012… Cosmetics were the most common substances causing relevant exposure found in both MCI/MI-allergic and MI-allergic patients."*

Lundov, M. D., Opstrup, M. S., & Johansen, J. D. (2013). **Methylisothiazolinone contact allergy - a growing epidemic**. *Contact Dermatitis*, *69*(5), 271-275. doi:10.1111/cod.12149

This context is especially important to include in the safety assessment so that manufacturers using these ingredients fully understand the public health impact of their choices. Also, there is even more recent data which shows that a restriction and/or ban on the use of MCI/MI in cosmetics has been very successful in significantly reducing the incidence of sensitization.

In response to the growing awareness of the epidemic of sensitization to these preservatives, the European Union banned MI in cosmetics in leave on cosmetics in 2016 and implemented a limitation of 15ppm in rinse-off cosmetics. Similarly, Australia implemented regulatory restrictions on MI and eventually banned it from leave-on cosmetics as well.

There are several recent papers, (only one of which is currently included in the CIR's Safety Assessment) which demonstrate the effectiveness of these bans and restrictions on public health.

For example in a recent study of data from the European Union**, the sensitization rate to MI decreased 50% between 2015 and 2017**.

Source: Uter W, Aalto-Korte K, Agner T, Andersen KE, Bircher AJ, Brans R, Bruze M, Diepgen TL, Foti C, Giménez Arnau A, Gonçalo M, Goossens A, McFadden J, Paulsen E, Svedman C, Rustemeyer T, White IR, Wilkinson M, Johansen JD; European Environmental Contact Dermatitis Research Group. The epidemic of methylisothiazolinone contact allergy in Europe: follow-up on changing exposures. J Eur Acad Dermatol Venereol. 2019 Aug 16. doi: 10.1111/jdv.15875.

A study from a hospital in Spain confirmed these results, finding that

"*regulatory interventions [on cosmetics] have resulted in a dramatic decrease in the prevalence of MCI and MI ACD, reaching a pre-epidemic level of 3.1% in 2019."*

Source: Magdaleno-Tapial, J., Valenzuela-Oñate, C., Ortiz-Salvador, J. M., García-Legaz-Martínez, M., Martínez-Domenech, Á., Alonso-Carpio, M., … Zaragoza-Ninet, V. (2019). Contact allergy to isothiazolinones epidemic: Current situation. Contact Dermatitis. doi:10.1111/cod.13396

A study in Germany reported on the "*unprecedented epidemic of MI-allergy mainly caused by its use in cosmetics*" and found that

"*Comparing sensitization to MI in three periods (2009, 2013/14 and 2017/18), there was an increase to 7% in 2013 and a decrease to 3.4% in 2018."*

Source: Schnuch, A., Schubert, S., Lessmann, H., & Geier, J. (2019). The methylisothiazolinone epidemic goes along with changing patients' characteristics – After cosmetics industrial applications are the focus. Contact Dermatitis. doi:10.1111/cod.13414

A study in Turkey found:

"In accordance with the recent reports, we also observed a decrease in the prevalence of MCI/MI and MI contact allergy from 2016 to 2018. This might be explained with the regulations made in Turkey as per European Commission cosmetics directive."

Source: Salman, A. (2018). Methylchloroisothiazolinone and methylisothiazolinone contact allergy: A retrospective cohort study from a tertiary dermatology clinic in Turkey. *Contact Dermatitis*. doi:10.1111/cod.13175

Lastly, in Australia, the sensitization rate to MI has also decreased nearly 50% between 2015 – 2017.

Source: Flury, U., Palmer, A., & Nixon, R. (2018). The methylisothiazolinone contact allergy epidemic in Australia. *Contact Dermatitis*, *79*(3), 189-191. doi:10.1111/cod.13025

Meanwhile in the U.S., there are no formal regulations restricting the use of MCI/MI, but instead the CIR's recommendations have been in place since 2014 – which does not recommend against the use of MI, but requires companies to use no more than 100ppm in rinse off products and to ensure a level in leave-on products that is non-sensitizing based on a QRA. Unlike the promising epidemiological data from the EU and Australia, the U.S. has not seen declines in sensitization to MI in recent years. According to the latest data from the NACDG in 2015-16, the sensitization rates for MI and MCI **were still increasing in the U.S.**

Source: DeKoven JG, Warshaw EM, Zug KA, Maibach HI, Belsito DV, Sasseville D, Taylor JS, Fowler JF Jr, Mathias CGT, Marks JG, Pratt MD, Zirwas MJ, DeLeo VA. (2018) North American Contact Dermatitis Group Patch Test Results: 2015-2016. Dermatitis. 2018 Nov/Dec;29(6):297-309. doi: 10.1097/DER.0000000000000417.

While I was pleased to see that the safety assessment now includes maximum recommended concentrations, it does not appear from the US data that the CIR's prior history of recommending that manufacturers in the U.S. formulate products to be non-sensitizing based on a QRA, has been successful in limiting or reversing the rising rates of sensitization to MCI/MI.

In order to see the same promising results in the US, as have been seen in the EU and Australia, I strongly recommend that the CIR also consider a determination that MCI/MI should not be used at any level in leave-on products.

For most decisions of the CIR, gathering evidence of actual health improvements that result from regulations on ingredients is relatively rare. In this case, the data is both clear and available. And the dermatological data on sensitization to isothiazilinones in the U.S. and elsewhere will continue to be collected every year and published. And the disparate results between countries that have implemented effective solutions to isothiazilinones and those that have not, will become more and more evident. The CIR will be held responsible for those disparate results in the U.S. based on their decision.

We now know that an epidemic of sensitization among the current generation could potentially have been avoided if the CIR had made a different decision on MCI/MI in cosmetics back in 1992. Now that a clear and successful path to reverse the trend of increasing sensitization has been forged in the EU and in Australia, the CIR has the opportunity to make that same significant difference to the health of Americans. Making the wrong decision means thousands of additional Americans, could be unnecessarily sensitized to isothiazilinones. This is a responsibility that the CIR must take very seriously.

Sincerely,

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

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: December 2, 2019
Subject: Draft Final Safety Assessment on *Punica granatum*-Derived Ingredients – Wave 2

Enclosed is a memo from the CIR Science and Support Committee (SSC) that provides comments concerning the current conclusion on the safety of *Punica granatum*-derived ingredients, specifically the insufficiency on data with regards to potential skin depigmentation. No data or comments were provided by the CIR SSC on any of the other data insufficiencies.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: November 19, 2019

SUBJECT: Tentative Amended Report: Safety Assessment of *Punica granatum* (Pomegranate)-Derived Ingredients as Used in Cosmetics (release date: September 30, 2019)

The CIR SSC appreciates the opportunity to comment on the tentative report, Safety Assessment of *Punica granatum* (Pomegranate)-Derived Ingredients as Used in Cosmetics.

Consistent with other CIR reports, such as the 2008 final report on licorice-derived ingredients, we believe that the potential skin depigmention effect reported for a number of pomegranate-derived materials can be addressed in the Discussion of the CIR report. The Discussion of the licorice report states: "Cosmetic formulators should only use licorice extracts in products in a manner that does not cause depigmentation."

We believe the studies summarized in the Skin Lightening section of the CIR report on pomegranate-derived ingredients identifies a potential hazard that is not relevant at the much lower levels of pomegranate-derived ingredients recently reported as used in cosmetics. For example, the *in vitro* study on a Punica Granatum Peel Extract containing 90% ellagic acid is on a material that would be given the INCI name Ellagic Acid rather than Punica Granatum Peel Extract. For comparison, one study[1] reports the total phenolic content of a dried pomegranate peel powder as 27.92% and the ellagic acid content as 44.19 mg/100 g dry matter (0.04419%). As presented in the CIR report, the human study reporting reduced melanin levels used 4% concentrated pomegranate juice in a formulation, in contrast to a maximum reported use concentration of 0.1% Punica Granatum Fruit Juice in makeup products.

[1] Rowayshed G, Salama A, Abul-Fadl M, et al. 2013. Nutritional and Chemical Evaluation for *Pomegranate* (*Punica granatum* L.) Fruit Peel and Seed Powders By Products. *Middle East Journal of Applied Sciences* 3(4): 169-179.

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It should also be noted that none of the suppliers of the *Punica granatum*-derived ingredients have requested that "skin bleaching agent" be included in the *International Cosmetic Ingredient Dictionary* as a function for these ingredients.

As with all plant extracts, these pomegranate-derived ingredients under review are variable in composition depending on many factors including growth conditions, plant part(s) used and method of manufacture. Because of the variability in composition of the pomegranate-derived ingredients, we are concerned that additional data trying to identify NOAELs for skin lightening effects for each INCI name would only apply to the material that was tested. In addition, the potential for an ingredient to contribute to skin depigmenting effects of a finished cosmetic product is dependent on the formulation, not just the concentration of one ingredient.

As was done in the licorice-derived ingredients report, the skin depigmentation issue should be addressed in the Discussion. The Discussion should make it clear that the CIR Expert Panel considers depigmentation of the skin to be an inappropriate effect of a cosmetic product and that cosmetic formulators should only use pomegranate-derived ingredients in products in a manner that does not cause depigmentation.