

# SUPPLEMENT

Polyaminopropyl Biguanide

Sultaines

Witch Hazel

CIR EXPERT PANEL MEETING  
SEPTEMBER 11-12, 2017



Cosmetic  
Ingredient  
Review

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Memorandum

To: CIR Expert Panel Members and Liaisons  
From: Wilbur Johnson, Jr.  
Senior Scientific Analyst  
Date: August 31, 2017  
Subject: Wave 2 Data on Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

The data listed below (in *polyam092017* data files) on Polyaminopropyl Biguanide were received from the Council and are being submitted as attachments to this memorandum. The data that were received include:

- Comments Received From Lonza, Inc. (*polyam092017pcpc2*)
- Quantitative Risk Assessment (QRA) Memorandum (*polyam092017data7*)
- QRA (*polyam092017data8*)
- QRA Worksheet (*polyam092017data9*)
- Mouse Developmental Toxicity Study (data clarification) (*polyam092017data10*)

The comments that were received from Lonza, Inc. address each item in the Insufficient Data Announcement (IDA) that was issued at the June 12-13, 2017 CIR Expert Panel (Panel) meeting, and the QRA was received from the Council in response to the Panel's request for a dermal sensitization QRA in the IDA.

In the August 18, 2017 memorandum to the Panel, it is noted that 2 different sources for the results of an Alderley Park mouse developmental toxicity study are included in Table 13 of the draft tentative report on Polyaminopropyl Biguanide. Different values for the maternal NOAEL and the developmental NOAEL are presented. The primary reference for this study was received from the Council in response to this concern, and errors in the data summary presented in Table 13 will be addressed.

After the Panel meeting, the issued report will be revised to include the data that were received and the corrected summary of the mouse developmental toxicity study.

## Memorandum

**TO:** Bart Heldreth, Ph.D., Interim Director  
COSMETIC INGREDIENT REVIEW (CIR)

**FROM:** Lonza Ltd.

**DATE:** August 22, 2017

**SUBJECT:** Polyaminopropyl Biguanide (PHMB): Response to the insufficient data announcement

Lonza's responses are provided after the data requests.

The Panel found that the data are insufficient to determine the safety of Polyaminopropyl Biguanide.

The data needs are:

Calculation of a margin of safety for Polyaminopropyl Biguanide inhalation exposure, using exposure data from the short-term (28 days) rat inhalation toxicity study and current use concentration data on Polyaminopropyl Biguanide in hair sprays, both included in the CIR safety assessment.

Please be aware that Lonza do not support use of Polyaminopropyl Biguanide in any applications which would result in inhalation exposure. This is also noted in the SCCS opinions of 18 June 2014 - revised 13 July 2015 (SCCS/1535/14) and 23 December 2016 - final version 7 April 2017 (SCCS/1581/16) which concludes that Polyaminopropyl Biguanide (PHMB) is not safe for consumers when used as a preservative in cosmetic spray formulations up to a concentration of 0.3%. We would be happy for the CIR to apply the same restriction, therefore we do not believe that inhalation exposure calculations are necessary.

Further clarification of urticaria reactions reported in SCCS reports on Polyaminopropyl Biguanide.

The SCCS opinions of 18 June 2014 - revised 13 July 2015 (SCCS/1535/14) and 23 December 2016 - final version 7 April 2017 (SCCS/1581/16) make no reference to urticaria reactions and therefore it is not understood what further information the CIR Panel require on this point. Please could the CIR Panel clarify where in the SCCS reports on Polyaminopropyl Biguanide they have found reference to urticaria? I note that the CIR Panel have made reference to the contact urticaria induced by polyhexamethylene guanidine phosphate (PHMG), however PHMG is not identical Polyaminopropyl Biguanide. Lonza is very aware of the toxicology of Polyaminopropyl Biguanide and has

been careful to develop use recommendations which help our customers formulate products that are safe for consumers to use. This is why there are no, or virtually no incidents of adverse effects from the use of Polyaminopropyl Biguanide over the last 50 years. The incidents seen in Korea following use of PHMG perhaps reflect a less conscientious approach to marketing and use of that substance. However, that should not be allowed to influence the decision making for Polyaminopropyl Biguanide.

Raw data sheets (i.e., individual scores during induction and challenge phases) on subjects evaluated in the HRIPT on a product containing 0.2% Polyaminopropyl Biguanide, that was provided by the Council.

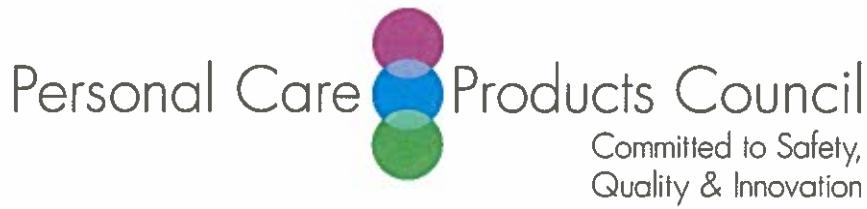
It is understood that this has already been submitted by the owner of the study.

A dermal sensitization quantitative risk assessment (QRA) for Polyaminopropyl Biguanide. Additionally, industry is encouraged to provide any available HRIPT data that can yield a more refined no-expected-sensitization-induction-level (NESIL); the current NESIL, at 25 µg/cm<sup>2</sup>, is likely to be overly conservative for use in the QRA.

We do not have any further data to provide you on this point. However, it should be noted that with respect to skin sensitization, the SCCS noted in their opinion: Based on various guinea pig maximization- and Buehler tests, PHMB can be considered a sensitizer in animals. The threshold for eliciting skin reactions or elicitation in guinea pigs is approximately 1 %. From HRIPT tests it can be concluded that a concentration of 2 % PHMB is capable of causing skin sensitisation in humans which can be elicited at concentrations starting from 0.2 % a.i. From reports on patch tests PHMB sensitization in humans can be considered of low frequency (up to 0.5 % in dermatitis patients). We believe this interpretation is valid and would urge the CIR Panel to reconsider the SCCS evaluation.

The Panel spent considerable time discussing issues relating to Polyaminopropyl Biguanide-induced anaphylaxis, sensitization, contact urticaria (confirmed in skin prick tests and blood tests for IgE levels) and lung injuries induced by polyhexamethylene guanidine phosphate, a chemical that is structurally similar to Polyaminopropyl Biguanide, though not identical. The latter issue is the basis for the Panel's request for a margin of safety calculation for Polyaminopropyl Biguanide inhalation exposure.

As stated above, Lonza do not support use of Polyaminopropyl Biguanide in any applications which would result in inhalation exposure.



## Memorandum

**TO:** Bart Heldreth, Ph.D., Interim Director  
COSMETIC INGREDIENT REVIEW (CIR)

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

**DATE:** August 16, 2017

**SUBJECT:** Polyaminopropyl Biguanide (PHMB)

Procter & Gamble. 2017. Polyhexamethylene biguanide hydrochloride (PHMB) exposure based quantitative risk assessment for contact dermatitis.

# Procter&Gamble

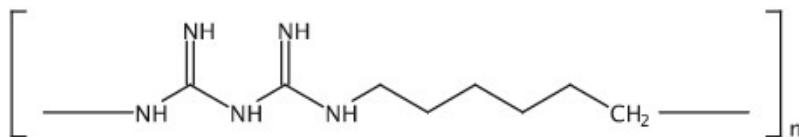
The Procter & Gamble Company  
Sharon Woods Innovation Center  
11530 Reed Hartman Highway, Cincinnati, Ohio 45241

To: Linda Loretz, Personal Care Products Council  
From: Don Bjerke, Petra Kern, and Cindy Ryan

15 August 2017

## Polyhexamethylene biguanide hydrochloride (PHMB) Exposure Based Quantitative Risk Assessment for Contact Dermatitis

Purpose: This memo provides an exposure-based quantitative risk assessment (QRA) for contact dermatitis with polyhexamethylene biguanide hydrochloride (CAS 32289-58-0; INCI name polyaminopropyl biguanide; PHMB) in cosmetics. This memo is intended to be shared with the Cosmetics Ingredient Review (CIR) Expert Panel, prior to the 144th meeting in Washington, DC on September 11-12, 2017. The QRA supports current reported use levels of PHMB in cosmetic products in all cases with the exception of an eye lotion product with 0.2% PHMB. We recommend a "safe as used" conclusion with regard to the skin sensitization endpoint for PHMB when formulated to be non-sensitizing.



• x HCl

Polyhexamethylene biguanide (CAS 32289-58-0)

PHMB Exposure Based QRA: The following sections review the animal and human PHMB skin sensitization data. From this data, a No Expected Sensitization Induction Level (NESIL) is derived. This NESIL is used in a QRA based on product type and maximum PHMB concentration data provided by PCPC as posted on the CIR website: [http://www.cir-safety.org/sites/default/files/polyaminopropyl%20biguanide\\_0.pdf](http://www.cir-safety.org/sites/default/files/polyaminopropyl%20biguanide_0.pdf), accessed 31 July 2017. Product consumer exposure data is derived from published literature (Api et al., 2008; IFRA RIFM QRA Information Booklet Version 7.1, July 2015). The Consumer Exposure Level (CEL) is derived from industry maximum use concentrations combined with habits and practices data for the cosmetic product type. In addition, the Acceptable Exposure Level (AEL) is calculated by dividing the NESIL by the Sensitization Assessment Factors (SAF). The SAFs are derived from the same references as the product exposure data and account for inter-individual variability, matrix differences between what was tested in the skin sensitization assays versus the product matrix, and to account for unique usage conditions. Finally, the AEL/CEL ratio is calculated to determine the margin of safety. If the AEL/CEL ratio is < 1, the usage concentration of PHMB cannot be supported under the defined product exposure conditions. If the AEL/CEL ratio is ≥ 1, then an adequate margin of safety exists to support product and preservative exposure conditions listed.

### Skin sensitization data:

Animal and human skin sensitization data indicates that PHMB is a weak skin sensitizer. Animal data includes 3 guinea pig maximization tests, 1 Buehler guinea pig test and 1 murine local lymph node assay (LLNA). Human data includes 4 Human Repeat Insult Patch Studies (HRIPT). Summary data is presented in table format followed by the derivation of the NESIL.

**Animal Skin Sensitization Data:**

| <b>Test Material,<br/>Concentration</b>   | <b>No. Animals</b>   | <b>Procedure</b>  | <b>Results</b>   | <b>Reference</b>   |
|---|--|---|--|--|
| <p><u>Test material:</u> Vantocil IB, a 20% solution of PHMB.</p> <p><u>Induction injection:</u> 1% Vantocil (0.2% PHMB).</p> <p><u>Topical induction:</u> Vantocil as supplied (20% PHMB).</p> <p><u>Challenge:</u> Vantocil as supplied (20% PHMB)</p>                                    | Control = 8 guinea pigs.<br><br>Treatment = 20 guinea pigs.  | Magnusson and Kligman Guinea Pig Maximization Test                | A total of 15/20 test animals (75%) had erythema scores of 1 or greater at either the 24 or 48 hour time point. A total of 1/8 control animals had a score of 1 at both 24 and 48 hours. Following the guidance provided in the ECETOC Technical Report No. 87 (reflected in Kimber et al., 2003), PHMB would be classified as a <b>weak contact allergen</b> .  | As reported in the SCCS review.<br>Study date = July 1980.     |
| <p><u>Test material:</u> a 20% aqueous solution of PHMB.</p> <p><u>Induction injection:</u> 0.3% test material (0.06% PHMB).</p> <p><u>Topical induction:</u> test material as supplied (20% PHMB).</p> <p><u>Challenge:</u> test material as supplied (20% PHMB) and at 30% (6% PHMB).</p> | Control = 10 guinea pigs.<br><br>Treatment = 20 guinea pigs. | Magnusson and Kligman Guinea Pig Maximization Test (OECD TG 406). | <p><b>20% PHMB Challenge:</b> A total of 18/20 test animals (90%) and 4/10 (40%) control animals had erythema scores of 1 or greater at either 24 or 48 hours. At 24 hours, 1 test animal had a score of 3 and 7 had scores of 2. The controls were limited to erythema scores of 1.</p> <p><b>6% PHMB Challenge:</b> A total of 5/20 test animals (25%) and 1/10 control animals (10%) had erythema scores of 1 or greater at either 24 or 48 hours.</p> <p>According to OECD TG 406, for adjuvant tests such as the GPMT, a response rate of 30% is considered to be a positive response, indicative of sensitization. Therefore, the 6% PHMB challenge results would be considered negative. Given that the 20% PHMB was somewhat irritating and the 6% PHMB was negative, a potency category cannot be assigned based on ECETOC TR No. 87. However, based on weight of evidence from this study, a <b>weak potency classification</b> can be considered.</p> | As reported in the SCCS review.<br>Study date = February 1993. |

|  |   |   |  |  |
|--|---|---|--|--|
| <p><u>Test material:</u> a 20% PHMB solution in saline.</p> <p><u>Intradermal injection:</u> 0.15% PHMB.</p> <p><u>Topical induction:</u> 20% PHMB.</p> <p><u>Challenge:</u> 20% PHMB or 10% PHMB.</p>   | <p>Control = 10 guinea pigs.</p> <p>Treatment = 10 guinea pigs.</p> | <p>Guinea Pig Maximization Test (OECD 406).</p> | <p><b>20% PHMB Challenge:</b><br/>A total of 1/10 test animals (10%) had moderate erythema at 24 hours. No reactions for control group.</p> <p><b>10% PHMB Challenge:</b><br/>A total of 1/10 test animals (10%) had moderate erythema at 24 and 48 hours. No reactions in control group.</p> <p>PHMB is <b>not considered as a dermal sensitizer</b> in this study according to the classification criteria.</p>  | <p>As reported in the SCCS review.<br/>Richeux, 2002c.</p>         |
| <p><u>Test material:</u> Vantocil IB, a 20% solution of PHMB.</p> <p><u>Topical induction:</u> 10% Vantocil (2% PHMB).</p> <p><u>Challenge:</u> 10% Vantocil (2% PHMB).</p> <p><u>Re-challenges:</u> 20%, 10% and 1% Vantocil (4%, 2%, and 0.2% PHMB).</p> | <p>Control = 10 guinea pigs.</p> <p>Treatment = 10 guinea pigs.</p> | <p>Buehler Guinea Pig Test</p>                  | <p><b>First Challenge:</b><br/>A total of 6/10 test animals (60%) had erythema scores of 1 or greater at 24 or 48 hours. No reactions in control group.</p> <p><b>Re-challenge 4% PHMB:</b> A total of 8/9 test animals (89%) and 3/10 controls (30%) responded to 4% PHMB with erythema scores of 1 or greater, suggesting that this concentration was irritating.</p> <p><b>Re-challenge 2% PHMB:</b> A total of 3/10 test animals (30%) responded with erythema while no control animals did (0/10).</p> <p><b>Re-challenge 0.2% PHMB:</b> No responses were observed in test animals or controls.</p> <p>According to ECETOC TR No. 87, a test material applied at an induction concentration 1-10% which has an incidence of positive responses <math>\geq 60\%</math> is classified as a moderate contact allergen. However, based on the re-challenge results with 2% PHMB which resulted in an incidence of positive responses from 15% up to 60%, PHMB in this study is classified as a <b>weak to moderate contact allergen</b>.</p> | <p>As reported in the SCCS review.<br/>Study date = July 1980.</p> |

|  |                 |                                |   |   |
|--|-----------------|--------------------------------|---|---|
| Polyhexamethylene biguanide (CAS 77785-50-9) | Not determined. | Murine local lymph node assay. | The company that ran the LLNA have indicated that this study should not be used for determining a NESIL (Linda Loretz, personal communication). | Gerberick et al., 2000 reported on an industry reported LLNA. |
|--|-----------------|--------------------------------|---|---|

**Human skin sensitization data:**

| Concentration  | No. Subjects  | Procedure   | Results  | Reference  |
|--|---|---|--|--|
| <u>Test material:</u><br>Vantocil IB, a 20% solution of PHMB.<br><br><u>Induction:</u> 10% Vantocil (2% PHMB; 2,500 µg/cm <sup>2</sup> ), 20% Vantocil (4% PHMB; 5,000 µg/cm <sup>2</sup> ).<br><br><u>Challenge:</u> 10% Vantocil (2% PHMB), 5% Vantocil (1% PHMB), 2.5% Vantocil (0.5% PHMB), 1% Vantocil (0.2% PHMB), 0.5% Vantocil (0.1% PHMB), 0.25% Vantocil (0.05% PHMB). | Preliminary Panel = 49 subjects.<br><br>Main Panel = 114 subjects.<br><br>Additional Panel = 29 subjects. | HRIPT with patch size = 2 cm x 2 cm (4cm <sup>2</sup> ). Dose volume = 0.5 mL.<br><br><u>Preliminary Panel:</u><br>Induction = first 6 patches at 2% PHMB, final 3 patches 4% PHMB.<br>Challenge at 2% PHMB. A total of 8/49 with positive reactions including strong erythema with marked edema or papules.<br><br><u>Main Panel:</u> Induction = first 3 patches 4% PHMB and final 6 patches 2% PHMB. Challenge at 0.5%, 0.2%, 0.1% and 0.05% PHMB. A total of 18/114 showed a positive response to 0.5% PHMB challenge; 7/114 showed a positive response to 0.2% PHMB challenge, and 0/114 reacted to 0.1% and 0.05% PHMB challenge.<br><br><u>Additional Panel:</u><br>Induction = 4-5 patches at 2% PHMB, remaining patches distilled water.<br>Challenges at 0.5%, 0.2%, 0.1%, and 0.05% PHMB.<br>A total of 1/29 showed a positive response to 0.5% challenge. All other subjects were negative. | Two different concentrations of PHMB were used in the induction phase of first two Panels. However, in the additional Panel 2% PHMB (2,500 µg/cm <sup>2</sup> ) was able to induce sensitization in 4-5 patches. It is not possible from this data to determine an exact NESIL. However, the <b>NESIL should be below 2,500 µg/cm<sup>2</sup>.</b> | CLH Report – PHMB – CAS 27083-27-8 or 32289-58-0, submitted 2010 in the scope of the Biocidal Product Directive for inclusion of the active substance PHMB in Annex I of directive 98/8/CE.<br><br>November 1981 |
| <u>Test material:</u> a 20% aqueous solution of PHMB diluted to 1% PHMB.   | 26 subjects.  | Adaptation of HRIPT. Induction occurred 3 times/week for 3-4 weeks (9 or 12 total patches). Skin patch moistened  | No subjects had a positive response at challenge. The study was only conducted in 26 subjects. <b>The</b>  | As reported in the SCCS review.<br>Hink, 1976  |

|   |               |   |   |   |
|---|---------------|---|---|---|
| <u>Induction:</u> 1% PHMB; 1,000 µg/cm <sup>2</sup> .<br><br><u>Challenge:</u> 1% PHMB.                               |               | with 0.4 mL of test solution. To increase skin penetration, sodium lauryl sulfate was added to a final concentration of 0.01%). Immediately after patch removal, the site was exposed to natural sunlight for one hour. Challenge occurred 6 weeks after initial exposure. During induction 1 individual had definite erythema following the 4 <sup>th</sup> and 5 <sup>th</sup> applications, and minimal erythema following the 3 <sup>rd</sup> and 6 <sup>th</sup> through the 12 <sup>th</sup> application. | <b>1% PHMB (1,000 µg/cm<sup>2</sup>) dose is considered a no-effect level.</b>  |   |
| <u>Test material:</u> neck cream containing 0.20% PHMB; 100 µg/cm <sup>2</sup> .                                      | 115 subjects. | Modified Draize HRIPT. 0.2 mL Test material applied to each 2 cm x 2 cm (4 cm <sup>2</sup> ) Parke-Davis Readi Bandagers for a 100 µg/cm <sup>2</sup> PHMB exposure.  | Generally transient, barely perceptible (0.5-level) to mild (1-level) patch test responses (specific and non-specific) on 43/115 or 37% of the test population during the induction and/or challenge phases of the study.<br><b>No meaningful irritation or allergic reactions.</b> | Reliance Clinical Testing Services, Inc. 2011.        |
| <u>Test material:</u> 0.5% solution of a trade name material containing 20% PHMB (0.1% PHMB; 25 µg/cm <sup>2</sup> .) | 207 subjects. | HRIFT with 0.1 g applied of solution containing 0.1% PHMB to 2 cm x 2 cm (4cm <sup>2</sup> ) occlusive patch for a dose metric of 25 µg/cm <sup>2</sup> applied.<br><br>9 induction patches for 48-72 hr patch duration over 3 weeks, followed by a 2 week rest period, then challenge patch at a naïve site and readings 24-96 hours following patch removal.  | No skin reactions were observed during the induction phase or following challenge patch testing. <b>No evidence of allergic skin reactions under the conditions of the study.</b>   | Study summary provided by PCPC and completed in 2011. |

Derivation of the NESIL for PHMB:

When conducting a QRA for skin sensitization, human data (when sufficient) is preferred over animal data and the relevant metric is dose per unit area of skin (Kimber et al., 2008). A number of non-clinical and clinical data for skin sensitization are available for PHMB, showing some skin sensitization effects. While there is a clear indication

for skin sensitization in both human and animal studies, it is difficult to set a NESIL for PHMB. Human HRIPT data demonstrated no evidence of sensitization at induction doses ranging from 25 µg/cm<sup>2</sup> to 1,000 µg/cm<sup>2</sup>, with induction of sensitization occurring in one HRIPT at 2,500 µg/cm<sup>2</sup>. Unfortunately, the HRIPT that was conducted at the highest non-sensitizing dose only had 26 subjects, which is less than the preferred number of 100 or more (McNamee et al., 2008). Medical surveillance data indicates that prevalence of PHMB sensitization is extremely rare, between 0.4% and 0.8% (Schnuch et al., 2000 and 2007). Thus, the probability of detecting a response with 26 subjects is reduced (McNamee et al., 2008) and animal data should be considered as part of the overall weight of evidence. Based on the animal data, the material is considered a weak sensitizer when tested at a topical induction concentration of 20% in guinea pig maximization tests and when tested at a topical induction concentration of 2% in the Buehler guinea pig test. Thus, taking a weight of the evidence approach that includes all of the testing data in both humans and animals, the weight of evidence (WoE) NESIL of 1,000 µg/cm<sup>2</sup> is chosen.

**Therefore, the WoE NESIL for polyhexamethylene biguanide hydrochloride (PHMB) is 1,000 µg/cm<sup>2</sup>.**

Derivation of CEL, AEL and AEL/CEL ratio: The PHMB Consumer Exposure Level (CEL), Acceptable Exposure Level (AEL), and margin of safety as defined by the AEL/CEL ratio are derived as indicated in the above section entitled PHMB Exposure Based QRA. The attached Excel spreadsheet has the QRA input data presented, along with the margin of safety (i.e., AEL/CEL ratio). The product type and maximum reported PHMB usage level was provided by the PCPC usage data listed on the CIR website. Product exposures and default Sensitization Assessment Factors (SAF) were derived from Api et al., 2008 and the IFRA RIFM QRA Handbook. Using the default assumptions, all of the cosmetic product types and reported usage levels provide an adequate margin of safety (i.e., AEL/CEL ≥ 1), with the exception of eye lotions with a PHMB concentration of 0.2% (highlighted in the Excel table in red). It should be noted that all reported cosmetic uses of PHMB that are supportable by the QRA are ≤ 0.1% PHMB, consistent with the favorable SCCS review of PHMB in cosmetics up to 0.1%. Given the low prevalence of PHMB skin sensitization, the fact that SCCS lowered the supportable concentration in cosmetics from 0.3% to 0.1%, and the fact that the QRA using a NESIL of 1,000 µg/cm<sup>2</sup> also supports use of PHMB concentrations at 0.1% and below, we feel confident that the NESIL and QRA are robust and sufficient to support current use levels of PHMB in cosmetics (with perhaps one exception).



Worksheet in  
PHMB QRA for CIR S

The eye lotion with a PHMB concentration of 0.2% PHMB has a default SAF for eye products as 300: 10X inter-individual variability, 3X matrix differences, and 10X for use conditions (Api et al., 2008). This eye lotion product does not support a favorable margin of safety using default exposure and SAF assumptions. Using the default exposure and SAF assumptions, the maximum level of PHMB in an eye lotion product that produces an adequate margin of safety is 0.15% PHMB. Thus, the manufacturer of the eye lotion product with 0.2% PHMB could either lower the concentration to less than or equal to 0.15% PHMB or provide a refined risk assessment that justifies a different consumer exposure level or refined SAFs.

**Recommendation:** We recommend a NESIL of 1,000 µg/cm<sup>2</sup> for PHMB in cosmetic products and a favorable review of “safe as used in current practices and concentrations when formulated to be non-sensitizing” for the skin sensitization endpoint as supported by the attached QRA.

References:

Api, AM, Basketter, DA, Cadby, PA, Cano, M-F, Ellis, G, Gerberick, GF, Griem, P, McNamee, PM, Ryan, CA, and Safford, R (2008). Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. *Regulatory Toxicology and Pharmacology* **52**:3-23.

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McNamee, PM, Api, AM, Basketter, DA, Gerberick, GF, Gilpin, DA, Hall, BM, Jowsey, I and Robinson, MK (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.

Personal Care Products Council. Concentration of use by FDA product category - Polyaminopropyl biguanide. Unpublished data submitted by the Personal Care Products Council on 4-11-2017. 2017. pp.1

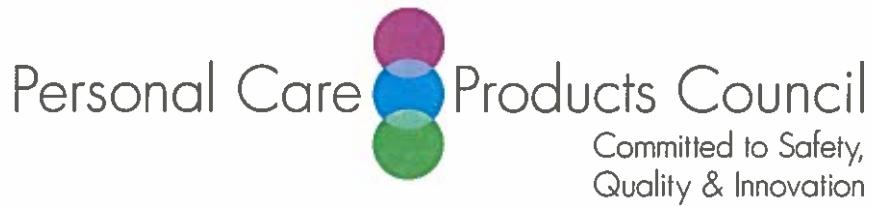
Schnuch, A, Geier, J, Brasch, J, Fuchs, T, Pirker, C, Schulze-Dirks, A and Basketter, DA (2000). Polyaminopropyl biguanide: A relevant contact allergen? *Contact Dermatitis* **42**:302-303.

Schnuch, A, Geier, J, Uter, W, Basketter, DA and Jowsey, IR (2007). The biocide polyaminopropyl biguanide remains an uncommon contact allergen. *Contact Dermatitis* **56**:235-239.

Scientific Committee on Consumer Safety (SCCS). Scientific Committee on Consumer Safety (SCCS) opinion on the safety of poly(hexamethylene) biguanide hydrochloride (PHMB).

[http://ec.europa.eu/health/scientific\\_committees/consumer\\_safety/docs/scos\\_o\\_157.pdf](http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/scos_o_157.pdf). Last Updated 2015. Date Accessed 07-31-2017.

| Product Category                                     | Max Use (%) | Product Exposure<br>(µg/cm <sup>2</sup> ) | PHMB CEL<br>(µg/cm <sup>2</sup> ) | PHMB NESIL (µg/cm <sup>2</sup> ) | SAF        | PHMB AEL     | AEL/CEL     | Reference for Exposure   |
|--|-------------|---|-----------------------------------|----------------------------------|------------|--------------|-------------|--|
| Baby lotions, oils, powders, creams                  | 0.1         | 2200                                      | 2.20                              | 1000                             | 300        | <b>3.33</b>  | 1.52        | IFRA RIFM QRA Information Booklet version 7.1 July 2015 (Category 3)           |
| Eye shadow   | 0.03        | 2170                                      | 0.65                              | 1000                             | 300        | <b>3.33</b>  | 5.12        | Api et al., 2008 Eye products.   |
| <b>Eye lotion</b>                                    | <b>0.2</b>  | <b>2170</b>                               | <b>4.34</b>                       | <b>1000</b>                      | <b>300</b> | <b>3.33</b>  | <b>0.77</b> | Api et al., 2008 Eye products.   |
| Eye makeup remover                                   | 0.056       | 900                                       | 0.50                              | 1000                             | 100        | <b>10.00</b> | 19.84       | Api et al., 2008 Make-up remover.  |
| Mascara  | 0.1         | 2170                                      | 2.17                              | 1000                             | 300        | <b>3.33</b>  | 1.54        | Api et al., 2008 Eye products.   |
| Other eye makeup                                     | 0.01        | 2170                                      | 0.22                              | 1000                             | 300        | <b>3.33</b>  | 15.36       | Api et al., 2008 Eye products.   |
| Hair conditioners                                    | 0.06        | 200                                       | 0.12                              | 1000                             | 100        | <b>10.00</b> | 83.33       | Api et al., 2008 Conditioners, rinse-off.                                      |
| Hair straighteners                                   | 0.01        | 4200                                      | 0.42                              | 1000                             | 100        | <b>10.00</b> | 23.81       | IFRA RIFM QRA Information Booklet version 7.1 July 2015 (Category 5, relaxers) |
| Shampoos (noncoloring)                               | 0.008       | 170                                       | 0.01                              | 1000                             | 100        | <b>10.00</b> | 735.29      | Api et al., 2008 Shampoos.   |
| Tonics, dressings and other hair grooming aids       | 0.1         | 990                                       | 0.99                              | 1000                             | 100        | <b>10.00</b> | 10.10       | Api et al., 2008 Hair styling aids   |
| Other noncoloring hair products                      | 0.002       | 1000                                      | 0.02                              | 1000                             | 100        | <b>10.00</b> | 500.00      | IFRA RIFM QRA Information Booklet version 7.1 July 2015 (Category 8).          |
| *Hair dyes and colors                                | 0.1         | 1000                                      | 1.00                              | 1000                             | 100        | <b>10.00</b> | 10.00       | IFRA/RIFM QRA Information Booklet version 7.1 July 2015, (Category 8).         |
| Foundations  | 0.01        | 3170                                      | 0.32                              | 1000                             | 100        | <b>10.00</b> | 31.55       | Api et al., 2008 Women's facial liquid makeup.                                 |
| Deodorants (underarm)                                | 0.003       | 8500                                      | 0.26                              | 1000                             | 300        | <b>3.33</b>  | 13.07       | Api et al., 2008 Solid AP.   |
| Other personal cleanliness products                  | 0.006       | 4400                                      | 0.26                              | 1000                             | 300        | <b>3.33</b>  | 12.63       | Api et al., 2008 Intimate wipes.   |
| Skin cleansing (cold creams, cleansing lotions, liqu | 0.1         | 900                                       | 0.90                              | 1000                             | 100        | <b>10.00</b> | 11.11       | Api et al., 2008 Make-up remover.  |
| Face and neck creams, lotions, powders and spray     | 0.02        | 2700                                      | 0.54                              | 1000                             | 100        | <b>10.00</b> | 18.52       | Api et al., 2008 Women's facial cream  |
| Body and hand creams, lotions and powders            | 0.009       | 1120                                      | 0.10                              | 1000                             | 300        | <b>3.33</b>  | 33.07       | Api et al., 2008 Body creams and lotions                                       |
| Moisturizers   | 0.00075     | 2700                                      | 0.02                              | 1000                             | 100        | <b>10.00</b> | 493.83      | Api et al., 2008 Women's facial cream  |
| Skin fresheners                                      | 0.0085      | 150                                       | 0.01                              | 1000                             | 100        | <b>10.00</b> | 784.31      | Api et al., 2008 Face washes, gels, scrubs.                                    |
| Suntan gels, creams, liquids                         | 0.1         | 2200                                      | 2.20                              | 1000                             | 100        | <b>10.00</b> | 4.55        | IFRA RIFM QRA Information Booklet version 7.1 July 2015 (Category 4)           |
| <b>Eye lotion with maximum supportable PHMB</b>      | <b>0.15</b> | <b>2170</b>                               | <b>3.26</b>                       | <b>1000.00</b>                   | <b>300</b> | <b>3.33</b>  | <b>1.02</b> | Api et al., 2008 Eye products.   |



## Memorandum

**TO:** Bart Heldreth, Ph.D., Interim Director  
COSMETIC INGREDIENT REVIEW (CIR)

**FROM:** Beth A. Jonas, Ph.D.  
Industry Liaison to the CIR Expert Panel

**DATE:** August 18, 2017

**SUBJECT:** Polyaminopropyl Biguanide (PHMB): Clarification of the mouse developmental toxicity study

Because of differences between the descriptions of the mouse developmental toxicity study (CTL/T/335) in the SCCS Opinions of 2014 and 2016, CIR staff requested to see the complete study.

An additional summary of this study with the following explanation has been provided: "The SCCS Opinion of 23 December 2016 - final version 7 April 2017 (SCCS/1581/16) incorrectly notes the following effects in the top dose group: maternal mortality, reduced food consumption, reduced body weight gain, pre- and post-implantation loss."

The Doc IIIA for the Biocidal Active Substance Polyhexamethylene Biguanide (PHMB) agreed by eCA France provides a further summary of the Teratogenicity Study in the Pregnant Mouse. Please see attached. This study summary was agreed by France and is the one reviewed by the SCCS. Clearly there has been some error in the finalisation of the SCCS 2017 Opinion."

Arch Chemicals, Inc. 2007. Biocidal active substance: Polyhexamethylene Biguanide: Summary of teratogenicity study in the pregnant mouse (Hodge et al. Central Toxicology Laboratory, Alderly Park, Report No: CTL/T/335, 1977).

|  |  |           |
|--|--|-----------|
| <b>Arch Chemicals Inc</b><br><b>(Trading as Arch UK Biocides Ltd.)</b> | <b>Biocidal active substance:</b><br><b>Polyhexamethylene Biguanide (PHMB)</b> | Page 1-9  |
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**Section A6.8.1/04      Teratogenicity Study in the Pregnant Mouse****Annex Point IIA, VI.6.8.1****Official  
use only****1      REFERENCE**

|   |  |
|---|--|
| <b>1.1      Reference</b>                         | <b>Doc IVA Code: ARCH A3-68-07.</b><br>Hodge, M. C. E., T. J. Iswaran, and S. Palmer. Baquacil SB: Teratogenicity Study in the Mouse. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Report No: CTL/T/335. April, 1977. |
| <b>1.2      Data protection</b>                   | Yes  |
| <b>1.2.1      Data owner</b>                      | Arch Chemicals, Inc.   |
| <b>1.2.2      Companies with letter of access</b> | None   |
| <b>1.2.3      Criteria for data protection</b>    | Data on existing as submitted for the first time for entry into Annex I  |

**2      GUIDELINES AND QUALITY ASSURANCE**

|                                 |     |
|---------------------------------|-----|
| <b>2.1      Guideline study</b> | No  |
| <b>2.2      GLP</b>             | No  |
| <b>2.3      Deviations</b>      | N/A |

**3      MATERIALS AND METHODS**

|                                       |   |
|---------------------------------------|---|
| <b>3.1      Test material</b>         | Polyhexamethylene Biguanide (PHMB)                            |
| <b>3.1.1      Lot/Batch number</b>    | Not reported  |
| <b>3.1.2      Specification</b>       | As given in section 2   |
| <b>3.1.2.1      Description</b>       | Not reported  |
| <b>3.1.2.2      Purity</b>            | 20 % w/w  |
| <b>3.1.2.3      Stability</b>         | Stable at ambient temperature in the dark.                    |
| <b>3.2      Test Animals</b>          |   |
| <b>3.2.1      Species</b>             | mouse   |
| <b>3.2.2      Strain</b>              | Not reported  |
| <b>3.2.3      Source</b>              | Specific pathogen-free colony at Alderley Park, Cheshire, UK  |
| <b>3.2.4      Sex</b>                 | Females   |
| <b>3.2.5      Age/weight at study</b> | 35 to 37 g on day 0 of gestation. Age not reported initiation |

|                           |  |           |
|---------------------------|--|-----------|
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**Section A6.8.1/04      Teratogenicity Study in the Pregnant Mouse****Annex Point IIA, VI.6.8.1**

|       |  |   |
|-------|--|---|
| 3.2.6 | Number of animals per group                | At least 21/group   |
| 3.2.7 | Control animals                            | Yes   |
| 3.2.8 | Mating period                              | Approximately 40 females were mated overnight Saturday to Wednesday each week until sufficient pregnancies were obtained. Two females were housed with one male and the following morning examined for vaginal plugs which were regarded as evidence of successful mating. The day when plugs were detected was termed Day 0 of gestation and on this day mated females were randomly allocated to the 4 experimental groups and weighed. |
| 3.3   | <b>Administration/Exposure</b>             | Oral  |
| 3.3.1 | Duration of exposure                       | Days 6 through 15 of gestation  |
| 3.3.2 | Postexposure period                        | Days 16 through 18 of gestation   |
| 3.3.3 | Type                                       | Gavage  |
| 3.3.4 | Dose levels                                | 10, 20, or 40 mg/kg bw  |
| 3.3.5 | Vehicle                                    | 0.5% aqueous solution of Tween 80   |
| 3.3.6 | Concentration in vehicle                   | Not reported  |
| 3.3.7 | Total volume applied                       | 0.1 ml per 10 g of body weight  |
| 3.3.8 | Controls                                   | Vehicle   |
| 3.4   | <b>Examinations</b>                        |   |
| 3.4.1 | Body weight                                | Yes. The bodyweight of each animal was recorded on days 0, 6, 8, 10, 12, 14, 16 and 18 of pregnancy.  |
| 3.4.2 | Food consumption                           | Yes. Food consumption was measured over each 6 day period.  |
| 3.4.3 | Clinical signs                             | Daily, although no record of each clinical sign and its subsequent course reported  |
| 3.4.4 | Examination of ovaries                     | Not reported  |
| 3.4.5 | Examination of uterus and uterine contents | Number of implantations, litter size and resorptions (early and late). Gravid uteri with cervix not reported. Number of corpora lutea not determined.   |
| 3.4.6 | Examination of foetuses                    | Foetal weight, litter weight, notation of external, visceral, and skeletal foetal abnormalities, assessment of ossification, and sex ratio. Dead foetuses not reported.   |

|                           |  |           |
|---------------------------|--|-----------|
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**Section A6.8.1/04      Teratogenicity Study in the Pregnant Mouse****Annex Point II A, VI.6.8.1****3.4.6.1 General**

The following maternal tissues were submitted for histopathological examination from 21 pregnant control animals and 21 pregnant high dose animals: lung, liver, kidney, ovary, uterus, placenta, stomach, duodenum, jejunum, ileum and mesenteric lymph node. Maternal tissues from the remaining animals in all groups were examined macroscopically. Abnormal tissues, or uterus and placenta in the case of foetal abnormalities, were also submitted for histological examination.

**3.4.6.2 Skeletal**

Yes

**3.4.6.3 Soft tissue**

Yes

**3.5 Further remarks**

In addition to the other reported deficiencies, there is no record of animal health given, and health status was not assessed. No indication is given as to the acclimation period, and poor health may have contributed to the low pregnancy rate (59%). Although general descriptions of external, soft tissue malformations was presented, no detailed individual animal record is reported. The temperature and relative humidity in the animal room was not reported, so there is no record on any fluctuations which may have affected animal health.

**4      RESULTS AND DISCUSSION**

- 4.1 Maternal toxic Effects** All animals, except for isolated, non-treatment related effects in 2 dams from group 2 (10 mg/kg) and 2 dams from group 3 (20 mg/kg), remained in good condition throughout the study and exhibited no clinical signs of toxicity. Mean bodyweight gain was similar in the control, 10 mg/kg and 20 mg/kg groups. There were more variable individual gains in the 40 mg/kg group than in other groups, resulting in a slightly reduced mean body weight gain which was not statistically significant.
- 4.2 Teratogenic / embryotoxic effects** Treatment with PHMB produced no adverse effects on any of the parameters measured (numbers of implantations, litter size, resorptions, foetal weight and litter weight) although numbers of early resorptions showed considerable variations between groups. Twenty one foetuses were found to have external abnormalities, but there was no evidence that the incidence of these findings was treatment-related. There were indications of slight retardation of ossification from examination of forelimb and hindlimb digits and numbers of cauda vertebrae in groups 3 and 4. The incidence of wide fontanelles and poorly ossified frontal bones in the skull, which were generally associated, also suggested retarded ossification in these groups although in this case the effects tended to be litter rather than treatment-related. There was no dose-related increase in abnormalities. The incidence of soft tissue abnormalities was not affected by treatment.
- 4.3 Other effects** The pregnancy rate was low, averaging 59%, in this experiment (expected value 80%). This was not due to PHMB administration since the pregnancy was low and similar in all groups. The sex ratio (males:females) was 0.89, 1.14, 0.91, and 0.90 for groups 1, 2, 3, and 4, respectively.

|                           |  |           |
|---------------------------|--|-----------|
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**Section A6.8.1/04      Teratogenicity Study in the Pregnant Mouse****Annex Point IIA, VI.6.8.1**

Very few abnormalities were observed at necropsy. Histopathological examination of the tissues which were submitted did not reveal any specific pathological effects that could be attributed to the administration of the test article.

**5      APPLICANT'S SUMMARY AND CONCLUSION**

- 5.1      Materials and methods** Groups of at least 21 pregnant mice were dosed orally by gavage with 0, 10, 20, or 40 mg PHMB/kg on days 6 through 15 of gestation. Maternal animals were evaluated for bodyweight changes, food consumption, clinical signs, and histopathological and gross pathological change to selected organs as noted above. The uterus was examined for number of implantations, litter size, and early and late resorptions. Foetuses were examined for individual bodyweight, litter weight, and external, visceral, and skeletal abnormalities.
- 5.2      Results and discussion** There were no clinical indications of maternal toxicity although maternal bodyweight gain was very slightly, but not statistically significantly, reduced at 40 mg/kg. Litter and foetal parameters, i.e. number of implantations, litter size, number of resorptions, foetal weight and litter weight were not affected by treatment, and there was no increase in the incidence of external, visceral, and skeletal abnormalities. Also, there was no gross or histopathological change to organs in the dams.
- 5.3      Conclusion** PHMB was neither teratogenic nor embryotoxic in the mouse. Doses of 20 and 40 mg/kg produce marginal retardation of ossification. This retardation was not observed at a dose of 10 mg/kg, and this dose is a no effect level.
- |   |   |
|---|---|
| <b>5.3.1      LO(A)EL maternal toxic effects</b>            | 40 mg/kg  |
| <b>5.3.2      NO(A)EL maternal toxic effects</b>            | 20 mg/kg  |
| <b>5.3.3      LO(A)EL embryotoxic / teratogenic effects</b> | 20 mg/kg  |
| <b>5.3.4      NO(A)EL embryotoxic / teratogenic effects</b> | 10 mg/kg  |
| <b>5.3.5      Reliability</b>                               | 3   |
| <b>5.3.6      Deficiencies</b>                              | The study was not conducted to any recognised guideline, and nor was it conducted to GLP. There is no record of the strain of animals used, nor any indication as to age at the time of the study. The temperature and relative humidity in the animal room was not reported, so there is no record on any fluctuations which may have affected animal health. There is no record of animal health given, and health status was not assessed. No indication is given as to the acclimation period, and poor health may have contributed to the low pregnancy rate (59%). Gravid uteri with cervix was not weighed.<br>For the maternal endpoints: |

|                           |  |           |
|---------------------------|--|-----------|
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**Section A6.8.1/04      Teratogenicity Study in the Pregnant Mouse****Annex Point IIA, VI.6.8.1**

- Number of corpora lutea was not determined
- The day of death of each dam was not given
- No record of the day of observation of each clinical sign and its subsequent course was provided
- A general description of maternal necropsy findings was provided; however, there was no detailed record, by animal, of the individual necropsy findings.
- Fetal endpoints
  - A general description of external, soft tissue and skeletal malformations was presented, but no individual record, by animal, was presented.

| <b>Evaluation by Competent Authorities</b>   |  |
|--|--|
|  | Use separate "evaluation boxes" to provide transparency as to the comments and views submitted   |
| <b>EVALUATION BY RAPPORTEUR MEMBER STATE</b> |  |
| <b>Date</b>                                  | <i>Give date of action</i>   |
| <b>Materials and Methods</b>                 | <i>State if the applicants version is acceptable or indicate relevant discrepancies referring to the (sub) heading numbers and to applicant's summary and conclusion.</i>  |
| <b>Results and discussion</b>                | <i>Adopt applicant's version or include revised version. If necessary, discuss relevant deviations from applicant's view referring to the (sub)heading numbers</i>   |
| <b>Conclusion</b>                            | Other conclusions:<br><i>(Adopt applicant's version or include revised version)</i>  |
| <b>Reliability</b>                           | <i>Based on the assessment of materials and methods include appropriate reliability indicator</i>  |
| <b>Acceptability</b>                         | acceptable / not acceptable<br><i>(give reasons if necessary, e.g. if a study is considered acceptable despite a poor reliability indicator. Discuss the relevance of deficiencies and indicate if repeat is necessary.)</i> |
| <b>Remarks</b>                               |  |
| <b>COMMENTS FROM ...</b>                     |  |
| <b>Date</b>                                  | <i>Give date of comments submitted</i>   |
| <b>Materials and Methods</b>                 | <i>Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.<br/>Discuss if deviating from view of rapporteur member state</i>                              |
| <b>Results and discussion</b>                | <i>Discuss if deviating from view of rapporteur member state</i>   |
| <b>Conclusion</b>                            | <i>Discuss if deviating from view of rapporteur member state</i>   |

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|                           |  |           |
|---------------------------|--|-----------|
|                           | <b>Biocidal active substance:</b><br><b>Polyhexamethylene Biguanide (PHMB)</b> | Page 6-9  |
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**Section A6.8.1/04      Teratogenicity Study in the Pregnant Mouse**

**Annex Point IIA, VI.6.8.1**

|                      |  |
|----------------------|--|
| <b>Reliability</b>   | <i>Discuss if deviating from view of rapporteur member state</i> |
| <b>Acceptability</b> | <i>Discuss if deviating from view of rapporteur member state</i> |
| <b>Remarks</b>       |  |
|                      |  |

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**Table A6.8.1/01-1. Intergroup Comparison of Maternal Performance, Clinical Findings, Body Weight, Food Consumption, and Post-Mortem Findings**

| Parameter   | Dose Level – mg/kg/day  |        |        |        | Dose-response<br>+/- |
|---|---|--------|--------|--------|----------------------|
|   | 0   | 10     | 20     | 40     |                      |
| Number of dams examined                                   | 26  | 29     | 21     | 28     |                      |
| Clinical findings during administration of test substance | No clinical findings at any dose that were different from the control group.    |        |        |        |                      |
| Macroscopic Findings Post-Mortem                          | No macroscopic findings at any dose that were different from the control group. |        |        |        |                      |
| Number not pregnant                                       | 20/49   | 17/47  | 24/49  | 17/48  | -                    |
| Pregnant  | 29/49   | 29/47  | 25/49  | 31/48  | -                    |
| Mortality   | 0/49  | 1/47   | 1/49   | 0/48   | -                    |
| Number littered   | 3/49  | 0/47   | 3/49   | 3/48   | -                    |
| Live foetuses in utero at termination                     | 26/49   | 29/47  | 21/49  | 28/48  | -                    |
| Body weight (g)   |   |        |        |        |                      |
| Day 0   | 35±4.6 <sup>a</sup>   | 37±5.1 | 37±5.3 | 37±5.1 | -                    |
| Day 6   | 39±3.9  | 40±4.7 | 41±5.8 | 41±4.5 | -                    |
| Day 8   | 41±3.9  | 41±4.1 | 42±5.7 | 42±4.3 | -                    |
| Day 10  | 43±4.2  | 44±4.3 | 44±5.5 | 45±4.3 | -                    |
| Day 12  | 48±3.9  | 48±5.0 | 49±6.2 | 49±5.5 | -                    |
| Day 14  | 52±4.1  | 52±6.0 | 52±6.6 | 52±6.7 | -                    |
| Day 16  | 58±5.1  | 59±7.0 | 58±7.3 | 57±7.7 | -                    |
| Day 18  | 65±6.7  | 65±8.4 | 65±8.3 | 63±9.6 | -                    |
| Pregnancy rate (%)  | 59  | 62     | 51     | 64     | -                    |

<sup>a</sup>Mean±SD from the number of dams examined as listed in each group

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**Table A6.8.1/01-2. Intergroup Comparison of Litter Data**

| Parameter                                  | Dose (mg/kg)          |            |            |            |
|--|-----------------------|------------|------------|------------|
|  | 0                     | 10         | 20         | 40         |
| <b>Number of Litters</b>                   | 26                    | 29         | 21         | 28         |
| <b>Number of Implantations/<br/>Litter</b> | 13.5±2.4 <sup>a</sup> | 13.2±3.2   | 13.2±2.5   | 13.0±4.2   |
| <b>Resorptions</b>                         |                       |            |            |            |
| <b>Early</b>                               | 63 (17.9%)            | 38 (9.9%)  | 27 (9.7%)  | 55 (16.3%) |
| <b>Late</b>                                | 5 (1.4%)              | 5 (1.3%)   | 2 (0.7%)   | 8 (2.2%)   |
| <b>Number of Viable<br/>Foetuses</b>       | 284                   | 340        | 248        | 296        |
| <b>Number of<br/>Foetuses/Litter</b>       | 10.9±2.9              | 11.7±3.0   | 11.8±2.8   | 10.6±4.0   |
| <b>Foetal Weight (g)</b>                   | 1.38±0.14             | 1.37±0.13  | 1.36±0.15  | 1.33±0.15  |
| <b>Litter Weight (g)</b>                   | 15.15±4.04            | 15.88±3.85 | 16.13±4.08 | 14.17±5.86 |

<sup>a</sup>Mean±SD

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**Table A6.8.1/01-3. Intergroup Comparison of Foetal Skeletal Variants Compared to Historical Control Data**

| Variant                            | Historical Controls |      | Dose of PHMB |      |     |      |      |      |      |      |
|------------------------------------|---------------------|------|--------------|------|-----|------|------|------|------|------|
|                                    |                     |      | 0            |      | 10  |      | 20   |      | 40   |      |
|                                    | No.                 | %    | No.          | %    | No. | %    | No.  | %    | No.  | %    |
| <b>Number of Animals Examined</b>  | 120                 |      | 107          |      | 108 |      | 113  |      | 115  |      |
| <b>Number of Foetuses Missing</b>  | 0                   |      | 0            |      | 1   |      | 0    |      | 1    |      |
| <b>Skull</b>                       |                     |      |              |      |     |      |      |      |      |      |
| Wide fontanelle                    | 5                   | 4.2  | 9            | 8.4  | 10  | 9.3  | 29** | 25.7 | 24** | 20.9 |
| Frontals partially ossified        | 7                   | 5.8  | 1            | 0.9  | 4   | 3.7  | 12** | 10.6 | 14** | 12.2 |
| Interparietals partially ossified  | 6                   | 5.0  | 0            | 0    | 1   | 0.9  | 5*   | 4.4  | 4    | 3.5  |
| <b>Sacral/Caudal</b>               |                     |      |              |      |     |      |      |      |      |      |
| 8 <sup>th</sup> Ossified           | 8                   | 6.7  | 24           | 22.4 | 19  | 17.6 | 13*  | 11.5 | 14*  | 12.2 |
| 9 <sup>th</sup> Ossified           | 11                  | 9.2  | 15           | 14.0 | 17  | 15.7 | 14   | 12.4 | 4*   | 3.5  |
| <b>Sternebrae</b>                  |                     |      |              |      |     |      |      |      |      |      |
| 5 <sup>th</sup> Partially ossified | 86                  | 71.7 | 28           | 26.2 | 45* | 41.7 | 56** | 49.6 | 38   | 33.0 |
| <b>3<sup>rd</sup></b>              |                     |      |              |      |     |      |      |      |      |      |
| Misaligned                         | 25                  | 15.8 | 7            | 6.5  | 18* | 6.7  | 16   | 14.2 | 16   | 13.9 |
| <b>4<sup>th</sup></b>              |                     |      |              |      |     |      |      |      |      |      |
| Misaligned                         | 32                  | 20.8 | 12           | 11.2 | 25  | 23.1 | 29*  | 25.7 | 21   | 18.3 |

\*Statistically significantly different from contemporaneous controls at the 5% level

\*\* Statistically significantly different from contemporaneous controls at the 1% level



Cosmetic  
Ingredient  
Review

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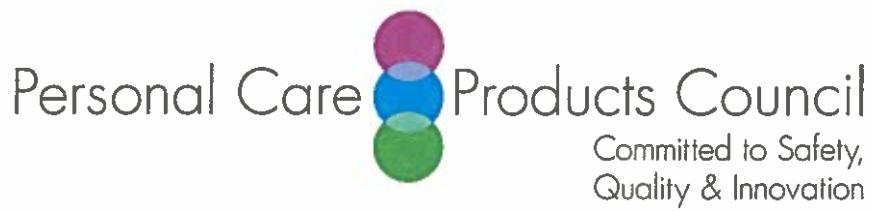
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Memorandum

To: CIR Expert Panel Members and Liaisons  
From: Christina L. Burnett, Senior Scientific Writer/Analyst  
Date: August 31, 2017  
Subject: Wave 2 – Sultaines

The Council has provided impurities data on Cocamidopropyl Hydroxysultaine and Lauramidopropyl Hydroxysultaine (*sultan092017data\_wave2*). A supplier reports that these ingredients contain approximately 50% solids. The 3,3-dimethylaminopropylamine (DMAPA) content is typically < 2 ppm for Cocamidopropyl Hydroxysultaine and < 3 ppm for Lauramidopropyl Hydroxysultaine.

This submission from the Council also contained additional in vitro ocular data on Cocamidopropyl Hydroxysultaine and Lauramidopropyl Hydroxysultaine (both tested at 4% solids): these ingredients were predicted to be mild to moderate eye irritants.



## Memorandum

**TO:** Bart Heldreth, Ph.D., Interim Director  
COSMETIC INGREDIENT REVIEW (CIR)

**FROM:** Beth A. Jonas, Ph.D.  
Industry Liaison to the CIR Expert Panel

**DATE:** August 24, 2017

**SUBJECT:** Cocamidopropyl Hydroxysultaine and Lauramidopropyl Hydroxysultaine

Colonial Chemical, Inc. reports that as sold to the cosmetics industry, Cocamidopropyl Hydroxysultaine and Lauramidopropyl Hydroxysultaine contain approximately 50% solids. For Cocamidopropyl Hydroxysultaine, DMAPA is typically <2 ppm. For Lauramidopropyl Hydroxysultaine, typical DMAPA values are <3 ppm.

Consumer Product Testing Co. 2014. The hen's egg test - utilizing the chorioallontoic membrane (HET-Cam) Cocamidopropyl Hydroxysultaine 4% solids.

Consumer Product Testing Co. 2017. The MatTek Corporation EpiOcular™ tissue model *in vitro* toxicity testing system Lauramidopropyl Hydroxysultaine 4% solids.



## FINAL REPORT

**CLIENT:** Colonial Chemical, Inc.  
225 Colonial Drive  
South Pittsburg, Tennessee 37380

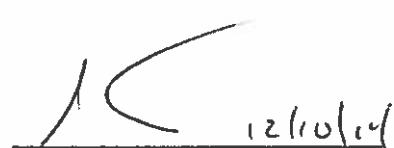
**ATTENTION:** Kacie Howard

**TEST:** The Hen's Egg Test - Utilizing the Chorioallantoic Membrane (HET-CAM)

**TEST ARTICLE:** ColaTeric CBS 4% Solids; Lot Number: 42615D14

*Cocamidopropyl Hydroxysulfate*

**EXPERIMENT  
REFERENCE NO.:** V14-5402-2



12/10/01  
Steven Nitka  
Vice President  
Laboratory Director

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## QUALITY ASSURANCE UNIT STATEMENT

Study No.: V14-5402-2

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of nonclinical laboratory studies. This study has been performed under Good Laboratory Practice principles (including government regulations to the extent applicable) and in accordance with standard operating procedures and applicable standard protocols. The QAU maintains copies of study protocols and standard operating procedures and has inspected this study on the date listed below. The findings of this inspection may have been reported to management and the Study Director.

Date of data inspection: 12/9/14

Quality Assurance:

Christine Hendricks 12/10/14  
Signature/Date

Colonial Chemical, Inc.  
V14-5402-2  
Page 3 of 6

**Objective:**

To evaluate the test article for irritancy potential utilizing the HET-CAM test. The test is a modification of that described by Kemper and Luepke.<sup>1</sup>

**Introduction:**

The chick embryo has been used extensively in toxicology. "The chorioallantoic membrane (CAM) of the chick embryo is a complete tissue with organoid elements from all germ cell layers. The chorionic epithelium is ectodermal and the allantoic epithelium is endodermal. The mesoderm located between these epithelia is a complete connective tissue including arteries, capillaries, veins and lymphatic vessels. The CAM responds to injury with a complete inflammatory reaction, comparable to that induced in the rabbit eye test. It is technically easy to study, and is without nerves to sense pain."<sup>2</sup>

**Test Article:** ColaTeric CBS 4% Solids; Lot Number: 42615D14

**Reference Articles:** Johnson's Baby Shampoo  
Head & Shoulders Shampoo

**Assay Date:** November 21, 2014

<sup>1</sup>Kemper, F.H. & Luepke, N.P., (1986). The HET-CAM Test: An Alternative to the Draize Test. *FD Chem. Toxic.* 24, p. 495 - 496.

<sup>2</sup>Leighton, J., Tchao, R., Verdone, J. & Nassauer, J. Macroscopic Assay of Focal Injury in the Chorioallantoic Membrane. In: *Alternative Methods in Toxicology*, Vol. 3, *In Vitro Toxicology* E2, pp. 357 - 369, Alan M. Goldberg, (ed.), Mary Ann Liebert Publishers, Inc., New York, 1985.

Colonial Chemical, Inc.  
V14-5402-2  
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**Method:**

White Leghorn eggs were obtained from Moyer's Chicks, Inc., in Quakertown, Pennsylvania. For incubation at this facility, the eggs were placed in a Kuhl, humidified incubator. The incubator is such that the eggs are automatically rotated once every hour. The temperature was controlled at 37° C ( $\pm 2^{\circ}$  C). On day eight (8) the eggs were turned so that the acutely angled end faced down.

On day ten (10) each egg was removed from the incubator and placed in a Plexiglas work enclosure. This enclosure had been preheated and humidified so that its environment approached that of the incubator. A cut was made in the larger end of each egg, where the air sack is located. A Dremel® Moto-Flex Tool (model 232-5) equipped with a Dremel® Cut-Off Wheel (No. 409) was used to make each cut. Forceps were then used to remove the shell down to the shell-membrane junction. The inner egg membrane was then hydrated with a warm, physiological saline solution. The saline was removed after a two (2) to five (5) minute exposure. Utilizing pointed forceps, the inner egg membrane was then carefully removed to reveal the CAM.

The test or reference article, at a dosage of three-tenths of one milliliter (0.3 ml) of a liquid or three-tenths of one gram (0.3 g) of a solid, was then administered to each of four (4) CAM's. Twenty seconds later, the test or reference article was rinsed from each CAM with five (5) milliliters of physiological saline. All CAM's were observed immediately prior to test article administration and at 30 seconds, two (2) and five (5) minutes after exposure to the test article. The reactions of the CAM, the blood vessels, including the capillaries, and the albumin were examined and scored for irritant effects as detailed below:

| Effect                               | Time (min.) | Score |   |   |
|--------------------------------------|-------------|-------|---|---|
|                                      |             | 0.5   | 2 | 5 |
| Hyperemia                            |             | 5     | 3 | 1 |
| Minimal Hemorrhage ("Feathering")    |             | 7     | 5 | 3 |
| Hemorrhage (Obvious Leakage)         |             | 9     | 7 | 5 |
| <u>Coagulation and/or Thrombosis</u> |             | 11    | 9 | 7 |

The numerical, time dependent scores were totaled for each CAM. Each reaction type can be recorded only once for each CAM, therefore the maximum score per CAM is 32. The mean score was determined for all CAM's similarly tested.

Colonial Chemical, Inc.  
V14-5402-2  
Page 5 of 6

**Results:**

| Test Article (%)                                    | CAM #           | Scores @ |        |              | Total |
|---|-----------------|----------|--------|--------------|-------|
|   |                 | 0.5 min. | 2 min. | 5 min.       |       |
| ColaTeric CBS 4% Solids; Lot Number: 42615D14 (50%) | 1               | 5 7      | 0      | 0            | 12    |
|   | 2               | 5 7      | 0      | 0            | 12    |
|   | 3               | 5 7      | 0      | 0            | 12    |
|   | 4               | 5 7      | 0      | 0            | 12    |
|   | <b>Average:</b> |          |        | <b>12.00</b> |       |

| Reference Article (%)        | CAM #           | Scores @ |        |              | Total |
|------------------------------|-----------------|----------|--------|--------------|-------|
|                              |                 | 0.5 min. | 2 min. | 5 min.       |       |
| Johnson's Baby Shampoo (50%) | 1               | 5 7      | 0      | 0            | 12    |
|                              | 2               | 5 7      | 0      | 0            | 12    |
|                              | 3               | 5 7      | 0      | 0            | 12    |
|                              | 4               | 5 7      | 0      | 0            | 12    |
|                              | <b>Average:</b> |          |        | <b>12.00</b> |       |

| Reference Article (%)          | CAM #           | Scores @ |        |              | Total |
|--------------------------------|-----------------|----------|--------|--------------|-------|
|                                |                 | 0.5 min. | 2 min. | 5 min.       |       |
| Head & Shoulders Shampoo (50%) | 1               | 5 7      | 0      | 5 7          | 24    |
|                                | 2               | 5 7      | 0      | 5 7          | 24    |
|                                | 3               | 5 7      | 7      | 0            | 19    |
|                                | 4               | 5 7      | 0      | 5            | 17    |
|                                | <b>Average:</b> |          |        | <b>21.00</b> |       |

Each article was then classified as indicated in the following:

| Mean Score  | Irritation Potential |
|-------------|----------------------|
| 0.0 - 4.9   | Practically none     |
| 5.0 - 9.9   | Slight               |
| 10.0 - 14.9 | Moderate             |
| 15.0 - 32.0 | Severe               |

Colonial Chemical, Inc.  
V14-5402-2  
Page 6 of 6

**Discussion:**

Previous studies have shown that the CAM of the hen's egg is more sensitive to liquid irritants than is the rabbit eye. Therefore, 50% dilutions of the liquid test and reference articles, in distilled water, were used.

**Historical *In Vivo* Results:**

The Johnson's reference product has historically been categorized as being moderately irritating, eliciting scores approaching 10, at 24 hours, when dosed at 100% and tested using the Draize ocular irritation methodologies (Draize Scale: 0 – 110). The Head & Shoulders reference product has historically been categorized as being severely irritating, eliciting scores approaching 30, at 24 hours, when dosed at 100% and tested using the Draize ocular irritation methodologies.

**Conclusion:**

Under the conditions of this test, the results indicate that the sponsor-submitted product, ColaTeric CBS 4% Solids; Lot Number: 42615D14, at 100%, would have a moderate ocular irritation potential *in vivo*.

**Record Retention:**

All records and documents pertaining to the conduct of this study shall be retained in the CPTC archives for a minimum of ten (10) years. At any time prior to the completion of the tenth archival year, a Sponsor may submit a written request to the CPTC QA Department to obtain custody of study records once the CPTC archive period has been completed. This transfer shall be performed at the Sponsor's expense. In the absence of a written request, study-related records shall be destroyed at the end of the CPTC archive period in a manner that renders them useless.

**Professional personnel involved:**

|                       |   |   |
|-----------------------|---|---|
| Steven Nitka, B.S.    | - | Vice President<br>Laboratory Director<br>(Study Director) |
| Lillian Vazquez, B.S. | - | Laboratory Supervisor                                     |
| Christine Hendricks   | - | Quality Assurance Group Leader                            |



## FINAL REPORT

**CLIENT:**

Colonial Chemical, Inc.  
225 Colonial Drive  
South Pittsburg, Tennessee 37380

**ATTENTION:**

Kacie Howard

**TEST:**

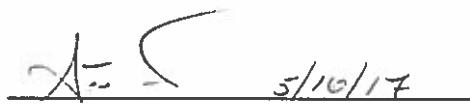
The MatTek Corporation EpiOcular™ Tissue Model *In Vitro* Toxicity Testing System

**TEST ARTICLE:**

ColaTeric LMHS 4% Solids, Lauramidopropyl Hydroxysultaine; Lot Number: KDM-1021-155

**EXPERIMENT  
REFERENCE NO.:**

V17-1919-1

  
Steven Nitka  
Vice President  
Laboratory Director

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Consumer Product Testing Co.

USA 1975

**QUALITY ASSURANCE UNIT STATEMENT**

**Study No.: V17-1919-1**

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of nonclinical laboratory studies. This study has been performed under Good Laboratory Practice principles (including government regulations to the extent applicable) and in accordance with standard operating procedures and applicable standard protocols. The QAU maintains copies of study protocols and standard operating procedures and has inspected this study on the date listed below. The findings of this inspection may have been reported to management and the Study Director.

**Date of data inspection:** 5/15/17

**Quality Assurance:**

Christopher Vanden 5/16/17  
Signature/Date

Colonial Chemical, Inc.  
V17-1919-1  
Page 3 of 6

**Objective:**

To evaluate the test article for irritancy potential utilizing the MatTek Corporation EpiOcular *in vitro* toxicity testing system.

**Introduction:**

"MatTek's patented EpiOcular corneal Model consists of normal, human-derived epidermal keratinocytes which have been cultured to form a stratified, squamous epithelium similar to that found in the cornea. The epidermal cells, which are cultured on specially prepared cell culture inserts using serum free medium, differentiate to form a multilayered structure which closely parallels the corneal epithelium . . . " This system " . . . provides a predictive, morphologically relevant *in vitro* means to assess ocular irritancy."<sup>1</sup>

EpiOcular, when used with the recommended cell metabolism assay, can quickly provide toxicological profiles. The procedure utilizes a water-soluble, yellow, tetrazolium salt (MTT {3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide}), which is reduced by succinate dehydrogenase in the mitochondria of viable cells to a purple, insoluble formazan derivative. Substances which damage this mitochondrial enzyme inhibit the reduction of the tetrazolium salt. The amount of MTT reduced by a culture is therefore proportional to the number of viable cells.

**Test Article:** ColaTeric LMHS 4% Solids, Lauramidopropyl Hydroxysultaine; Lot Number:  
KDM-1021-155

**Reference Article:** Triton X-100 (0.3%) (Positive Control)

**Experimental Interval:** May 3, 2017 to May 4, 2017

**Method:**

The test article, at 100%, exhibits a specific gravity greater than 0.95 g/ml. Therefore, as per MatTek's protocol, the test article was diluted to 20% in distilled water. After the appropriate tissue preparation, 100 microliters of the test article, the positive control article and the negative control (distilled water) were added to the Millicells containing the EpiOcular samples.

<sup>1</sup> MatTek Corporation, 200 Homer Avenue, Ashland, Massachusetts 01721

Colonial Chemical, Inc.  
V17-1919-1  
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**Method (continued):**

The six (6) well plates containing the dosed EpiOcular samples were then incubated at 37°C, five (5)% carbon dioxide and ≥ 90% humidity. After the appropriate exposure period, each insert was individually removed from its plate and rinsed with phosphate buffered saline (PBS) to remove any residual material. Each was then rinsed a second and third time. Following the 3 rinses, each Millicell was submerged in 5 milliliters of assay media for 10 minutes, at room temperature. This final soak removed any residual, absorbed article. After the 10 minutes, excess liquid was shaken off and each EpiOcular tissue was placed into 300 microliters of MTT solution. The EpiOcular samples were then returned to the incubator.

After the three (3) hour MTT exposure, each insert was removed and gently rinsed with PBS to remove any residual MTT solution. Excess PBS was shaken from each of the inserts, which were then blotted on the bottom using paper towels. The inserts were then each placed into one (1) well of a 24 well extraction plate. Each insert was then immersed in two (2) milliliters of extraction, at room temperature, overnight. After the extraction procedure, the liquid within each insert was decanted back into the well from which it was taken. The remaining extractant solution was then agitated and a 200 microliter aliquot of each extract was removed for evaluation. A Molecular Devices SpectraMax M5 Microplate Reader was used to determine the absorbance of each extract at 570nm. With the absorbance of the negative control (distilled water) defined as 100%, the percent absorbencies of the article were determined. The percentages listed below directly correlate with the cell metabolism in the EpiOcular samples.

**Results:**

| <u>Article<br/>(% &amp; Exposure)</u>  | <u>System</u> | <u>Percent<br/>Viability</u> | <u>Percent<br/>Inhibition</u> |
|--|---------------|------------------------------|-------------------------------|
| ColaTeric LMHS 4% Solids,<br>Lauramidopropyl Hydroxy-<br>sultaine; Lot Number:<br>KDM-1021-155 |               |                              |                               |
| (20% - 4 hrs.)   | EpiOcular     | 4                            | 96                            |
| (20% - 1 hr.)  | EpiOcular     | 15                           | 85                            |
| (20% - 20 mins.)   | EpiOcular     | 41                           | 59                            |
| Triton X-100   |               |                              |                               |
| (0.3% - 1 hr.)   | EpiOcular     | 20                           | 80                            |
| (0.3% - 20 mins.)  | EpiOcular     | 50                           | 50                            |
| (0.3% - 5 mins.)   | EpiOcular     | 89                           | 11                            |

Colonial Chemical, Inc.  
V17-1919-1  
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**Results (continued):**

When possible, using a semi-log scale, the percent viabilities for the article were plotted on the linear y axis versus the dosing time on the log x axis. By interpolation, the time at which the percent viability would be 50% was determined (ET-50). As a general guideline (provided by MatTek) the following equation can be used to estimate the rabbit Draize eye score:

$$\text{Draize} = -4.74 + 101.7/(\text{ET-50})^{0.5}$$

Based on the literature (Kay, J.H. and Calandra, J.C., "Interpretation of eye irritation tests," *J. Soc. Cosmetic Chem.*, 13, 281-289 (1962)), the ocular irritancy estimated potential has been categorized by MatTek into the following groups, based on the Draize score:

| <u>Draize Score</u> | <u>Irritancy Classification</u> | <u>Example</u>            | <u>EpiOcular ET-50 (min)</u> |
|---------------------|---------------------------------|---------------------------|------------------------------|
| 0-15                | Non-irritating, Minimal         | PEG-75 Lanolin, Tween 20  | >256 – 26.5                  |
| 15.1 – 25           | Mild                            | 3% Sodium Dodecyl Sulfate | <26.5 – 11.7                 |
| 25.1 – 50           | Moderate                        | 5% Triton X-100           | <11.7 – 3.45                 |
| 50.1 – 110          | Severe, Extreme                 | 5% Benzalkonium Chloride  | <3.45                        |

**Discussion:**

Under the conditions of this test, the ColaTeric LMHS 4% Solids, Lauramidopropyl Hydroxysultaine; Lot Number: KDM-1021-155 test article, at 20%, elicited *in vitro* results which indicate that its ET-50 is 14.0 minutes. Therefore, at 100%, the test article's estimated Draize ocular irritation score is approximately 22.44 with a "mildly irritating" irritancy classification. The Triton X-100 reference/positive control article elicited *in vitro* results which place its ET-50 at 20.1 minutes. Therefore the reference article's estimated Draize ocular irritation score is "18.0" with a "mildly irritating" irritancy classification.

**Conclusion:**

Under the conditions of this test, the results indicate that the ColaTeric LMHS 4% Solids, Lauramidopropyl Hydroxysultaine; Lot Number: KDM-1021-155 test article, at 100%, has a "mildly irritating" irritancy classification.

Colonial Chemical, Inc.  
V17-1919-1  
Page 6 of 6

**Record Retention:**

All records and documents pertaining to the conduct of this study shall be retained in the CPTC archives for a minimum of ten (10) years. At any time prior to the completion of the tenth archival year, a Sponsor may submit a written request to the CPTC QA Department to obtain custody of study records once the CPTC archive period has been completed. This transfer shall be performed at the Sponsor's expense. In the absence of a written request, study-related records shall be destroyed at the end of the CPTC archive period in a manner that renders them useless.

**Professional personnel involved:**

|                       |   |   |
|-----------------------|---|---|
| Steven Nitka, B.S.    | - | Vice President<br>Laboratory Director<br>(Study Director) |
| Lillian Vazquez, B.S. | - | Laboratory Supervisor                                     |
| Christine Vornehm     | - | Quality Assurance Compliance Specialist                   |
| William Cavaliere     | - | Quality Assurance Group Leader                            |



Cosmetic  
Ingredient  
Review

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## MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.  
Scientific Analyst and Writer

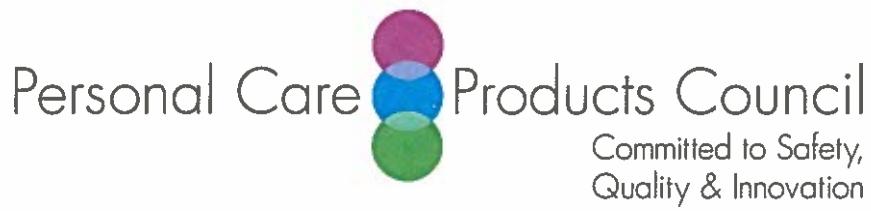
Date: August 31, 2017

Subject: Additional Data for *Hamamelis virginiana* (Witch Hazel)-Derived Ingredients As Used In Cosmetics

Attached herein are additional data on *Hamamelis virginiana* (Witch Hazel)-Derived Ingredients as used in cosmetics. This data includes:

- An HRIPT of a trade name mixture that contains Hamamelis Virginiana (Witch Hazel) Leaf Extract (6%) with negative results for irritation and sensitization [HamVir092017Data\_1]
- An Ames test of a trade name mixture that contains Hamamelis Virginiana (Witch Hazel) Leaf Extract (6%) with negative results [HamVir092017Data\_1]
- An *in vitro* phototoxicity assay of a trade name mixture that contains Hamamelis Virginiana (Witch Hazel) Leaf Extract (6%) with negative results. [HamVir092017Data\_1]  
The above are the only data on Hamamelis Virginiana (Witch Hazel) Leaf Extract (used up to 0.011%).
- An HRIPT of a product that contains Hamamelis Virginiana (Witch Hazel) Water (6.88%) with negative results for sensitization. [HamVir092017Data\_2] This HRIPT is at a lower concentration than what was already in the report (25.8%), but both are below the maximum concentration of use (43%).
- Concentration of Use data were updated with the following changes: Hamamelis Virginiana (Witch Hazel) Water in non-spray deodorants changed from 6% to up to 5.2% (does not change the maximum concentration of use); added Hamamelis Virginiana (Witch Hazel) Extract in a skin freshener at up to 86% (does not change the maximum concentration of use); Hamamelis Virginiana (Witch Hazel) Leaf Water paste masks and

mud packs concentration range changed from 4.1%-5% to up to 0.67%-4.1% (does not change the maximum concentration of use). [*HamVir092017Data\_3,4*]



## Memorandum

**TO:** Bart Heldreth, Ph.D., Interim Director  
COSMETIC INGREDIENT REVIEW (CIR)

**FROM:** Beth A. Jonas, Ph.D.  
Industry Liaison to the CIR Expert Panel

**DATE:** August 15, 2017

**SUBJECT:** Hamamelis Virginiana (Witch Hazel) Leaf Extract

BASF. 2015. Information on toxicological data for a trade name mixture containing Hamamelis Virginiana Leaf Extract.



We create chemistry

## Information on Toxicological Data

**Lys'Sun BC 10006**

PRD 30579765

Valid since 02.12.2015

Page 1 of 3

® = Registered trademark of BASF

™ = Trademark of BASF

Care Chemicals

**Product:****Lys'Sun BC 10006****CAS No.:**

7732-18-5, 84696-19-5, 5343-92-0, 1117-86-8, 11138-66-2

**INCI name:**

Aqua, Hamamelis Virginiana Leaf Extract, Pentylen Glycol, Caprylyl Glycol, Xanthan Gum

**GENERAL:**

This toxicological data summary refers exclusively to the product Lys'Sun BC 10006 in the quality as specified and provided by BASF. The toxicological data were generated with the substance ATOX 163A having the same composition than Lys'Sun BC 10006 but with a higher content of Hamamelis Virginiana Leaf Extract.

*ATOX 163 A contains 6% Hamamelis Virginiana Leaf Extract*

**1) SENSITIZATION and IRRITATION:**

Not sensitizing and not irritating (1)

## Test method:

Human Repeated Insult Patch Test

## Test conditions:

- Species:
- Number of volunteers:
- Test substance:
- Concentration:
- Duration of treatment:

Human volunteers

108

ATOX 163A

Diluted (7,5% in water)

The material was applied to the upper back and remained for 24 hours under semi-occlusive conditions. A total of 9 applications were applied for the induction. Following a 2-week rest period, the challenge patches were applied on the previously untreated test site.

After patch removal

No reactions were observed. The substance was rated to be a non-irritant and non-sensitizer in humans.

- Readings:
- Findings:



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## Information on Toxicological Data

**Lys'Sun BC 10006**

PRD 30579765

Valid since 02.12.2015

Page 2 of 3

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Care Chemicals

In addition, an eye irritation potential is not considered under use conditions due to the fact that no irritation was observed in the human skin irritation study, the absence of a classification of Lys'Sun BC 10006 with regard to eye irritation and the low concentration of the ingredients under use conditions.

**2) GENETIC TOXICITY****Bacterial Reverse Mutation Assay****No evidence for genetic mutation potential (2)**

Test method:

Ames

Test conditions:

- Strains:
- Test substance:
- Metabolic activation:
- Vehicle:
- Test concentrations:
- Findings:

TA98, TA 00, TA1537, TA1535, E.coli WP2 uvrA  
 ATOX 163A  
 S-9 Mix  
 water  
 333 - 66666 µg/plate

A weak bacteriotoxic effect was occasionally observed depending on the strain and test conditions about 33333 µg/plate.  
 The test substance did not induce any increase in the number of revertant colonies for any of the tester strains in the presence or absence of S-9 mix.

**3) PHOTOTOXICITY TEST:****not phototoxic (3)**

Test method:

OECD No. 432

Test conditions:

- Cell system:
  - UVA dose:
  - Test substance:
- Balb/c 3T3 cells  
 UVA Dose: 5 J/cm<sup>2</sup>  
 ATOX 163A



We create chemistry

## Information on Toxicological Data

### Lys'Sun BC 10006

PRD 30579765

Valid since 02.12.2015

Page 3 of 3

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- |                        |   |
|------------------------|---|
| - Test concentrations: | Up to 17000 µg/mL with and without irradiation<br>(5 J/cm <sup>2</sup> UVA)   |
| - Findings             | In the absence and presence of UVA<br>irradiation, no cytotoxicity was observed up to<br>the highest concentration. |

#### COMMENTS

The data are based on our current knowledge and are not claimed to be complete. The data do not relieve the user from the responsibility to check the suitability of the product for the intended use and from a risk assessment of its own products.

Our data may only be quoted with the consent of BASF.

#### REFERENCES

- (1) internal data (2013), HRIPT ATOX 163A
- (2) internal data (2013), ref. no. 40M0730/12M329
- (3) internal data (2013), ref. no. 20V0730/12M328

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Care  
Creations.



**Memorandum**

**TO:** Bart Heldreth, Ph.D., Interim Director  
COSMETIC INGREDIENT REVIEW (CIR)

**FROM:** Beth A. Jonas, Ph.D.  
Industry Liaison to the CIR Expert Panel

**DATE:** August 28, 2017

**SUBJECT:** Hamamelis Virginiana (Witch Hazel) Water

TKL Research. 2013. Repeated insult patch test of a toner containing 6.88% Hamamelis Virginiana (Witch Hazel) Water.



**REPEATED INSULT PATCH TEST**

Toner containing 6.88% Hamamelis Virginiana  
(Witch Hazel) Water  
TKL STUDY NO. DS108313-8

**CONDUCTED FOR:**

[REDACTED]  
[REDACTED]  
[REDACTED]

Attention: [REDACTED]

**DATE OF ISSUE:**

September 27, 2013

201.587.0500 • [www.tklresearch.com](http://www.tklresearch.com)

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## SIGNATURES

This study was conducted in compliance with the requirements of the protocol and TKL's Standard Operating Procedures, and in the spirit of GCP ICH Topic E6.<sup>1</sup> The report accurately reflects the raw data for this study.

Jonathan S. Dosik, MD  
Dermatologist  
Principal Investigator

Date

7/24/13

  
Kathleen Georgeian  
Director, Dermatologic Safety Testing

Date

9/24/13

  
Michelle Medina  
Manager, Dermatologic Safety Testing

Date

GBS/13

## STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

<sup>1</sup> ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

**TITLE OF STUDY**

Repeated Insult Patch Test

**SPONSOR**



**STUDY MATERIAL**

855167                  Toner

**DATE STUDY INITIATED**

July 29, 2013

**DATE STUDY COMPLETED**

September 6, 2013

**DATE OF ISSUE**

September 27, 2013

**INVESTIGATIVE PERSONNEL**

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## SUMMARY

One study material, Formula No. 855167, was evaluated neat to determine its ability to sensitize the skin of volunteer subjects with normal skin using an occlusive repeated insult patch study. One hundred ninety-nine (199) subjects completed the study, a deviation from the protocol-specified requirement of 200 completed subjects.

Under the conditions employed in this study, there was no evidence of sensitization to Formula No. 855167.

## 1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated topical applications to the skin of humans under controlled patch study conditions.

## 2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of TKL Research, Inc. These interpretive criteria are periodically reviewed and amended as new information becomes available.

## 3.0 STUDY DESIGN

### 3.1 STUDY POPULATION

A sufficient number of subjects were to be enrolled to provide 200 completed subjects. In the absence of any sensitization reactions in this sample size (200 evaluable subjects), a 95% upper confidence bound on the population rate of sensitization would be 1.5%.

#### 3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. Were males or females, 18 to 70 years of age, in general good health;
2. Were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events (AEs);
3. Were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;
4. Had completed a medical screening procedure; and
5. Had read, understood, and signed an informed consent (IC) agreement.

#### 3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. Had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;

2. Were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;
3. Had psoriasis and/or active atopic dermatitis/eczema;
4. Were females who were pregnant, planning to become pregnant during the study, or breast-feeding;
5. Had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated; and/or
6. Were participating in another study or had been recruited to participate in another study concurrently.

### 3.1.3 Informed Consent

A properly executed IC document was obtained from each subject prior to entering the study. The signed IC document is maintained in the study file. In addition, the subject was provided with a copy of the IC document (see Appendix III).

## 3.2 DESCRIPTION OF STUDY

### 3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application.<sup>2</sup>

Following the 9<sup>th</sup> evaluation, the subjects were dismissed for a Rest Period of approximately 10-15 days.

Subjects who were absent once during the Induction Phase received a make-up (MU) patch at the last induction visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading).

The Challenge Phase was initiated during the 6<sup>th</sup> week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after

<sup>2</sup> A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Rechallenge was performed whenever there was evidence of possible sensitization.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during Induction, and a single application and 2 readings at Challenge. Only completed cases were used to assess sensitization.

### 3.2.2 Study Flow Chart

#### WEEK 1

##### DAY ACTIVITIES

- 1<sup>3</sup> Staff obtained informed consent, reviewed completed medical screening form, applied patches
- 2 Subject removed patches
- 3 Staff graded sites, applied patches
- 4 Subject removed patches
- 5 Staff graded sites, applied patches
- 6 Subject removed patches

#### WEEK 2

##### DAY ACTIVITIES

- 1 Staff graded sites, applied patches
- 2-6 Same as Week 1

#### WEEK 3

##### DAY ACTIVITIES

- 1-6 Same as Week 2

#### WEEK 4

##### DAY ACTIVITIES

- 1 Staff graded sites; applied make-up (MU) induction patches, if required
- 2 Subject removed MU patches
- 3 Staff graded MU induction sites at MU visit
- 2-7 Rest Period

#### WEEK 5

##### DAY ACTIVITIES

- 1-7 Rest Period

---

<sup>3</sup> Study flow starting with Week 1, Day 1, was altered when enrollment occurred on Wednesday or Friday.  
Study flow could be altered if a holiday occurred during the study.

**WEEK 6****DAY ACTIVITIES**

- 1 Staff applied patches
- 2 Subject removed patches
- 3 Staff graded sites
- 4 Staff graded sites

**3.2.3 Definitions Used for Grading Responses**

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

**SYMBOL REACTION**

- = No reaction
- ? = Minimal or doubtful response, slightly different from surrounding normal skin
- + = Definite erythema, no edema
- ++ = Definite erythema, definite edema
- +++ = Definite erythema, definite edema and vesiculation

**SPECIAL NOTATIONS**

- E = Marked/severe erythema
- S = Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)
- p = Papular response > 50%
- pv = Papulovesicular response > 50%
- D = Damage to epidermis: oozing, crusting and/or superficial erosions
- I = Itching
- X = Subject absent
- PD = Patch dislodged
- NA = Not applied
- NP = Not patched (due to reaction achieved)
- N9G = No ninth grading

**3.2.4 Evaluation of Responses**

All responses were graded by a trained dermatologic evaluator meeting TKL's strict certification requirements to standardize the assignment of response grades.

## 4.0 NATURE OF STUDY MATERIAL

### 4.1 STUDY MATERIAL SPECIFICATIONS

Identification : 855167 Toner  
Amount Applied : 0.2 mL

### 4.2 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by TKL. On the basis of information provided by the Sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. All study material was kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was discarded or returned to the Sponsor and the disposition documented in the logbook.

### 4.3 APPLICATION OF STUDY MATERIAL

All study material was supplied by the Sponsor. Material was applied in an amount proportionate to the patch type or as requested by the Sponsor, generally 0.2 mL or g or an amount sufficient to cover the 2 cm x 2 cm patch. The patches were applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm.

### 4.4 DESCRIPTION OF PATCH CONDITIONS

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patches are secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad. The pads are affixed to the skin with hypoallergenic tape (Micropore).

## 5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the Challenge Phase of a Repeated Insult Patch Test (RIPT) than that seen during Induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours.

Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the Challenge Phase is generally similar to that seen during Induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. Our preferred Rechallenge procedure involves the application of the product to naive sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

## 6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) were designed to identify each subject by subject number and initials, and to record demographics, examination results, AEs, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage was maintained either at a TKL facility in a secured room accessible only to TKL employees, or at an offsite location which provided a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the Sponsor's review on the premises of TKL.

## 7.0 RESULTS AND DISCUSSION

Two hundred eleven (211) subjects between the ages of 18 and 70 were enrolled and 199 subjects completed the study, a deviation from the protocol-specified requirement of 200 subjects (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II). The following table summarizes subject enrollment and disposition.

|                       |     |
|-----------------------|-----|
| Number enrolled:      | 211 |
| Number discontinued:  | 12  |
| Lost to follow-up:    | 10  |
| Voluntary withdrawal: | 2   |
| Number completed:     | 199 |

Source: Table 1, Appendix I

There were no adverse events (AEs) reported during these studies.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

## 8.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to Formula No. 855167.

## 9.0 REFERENCES

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## **Memorandum**

**TO:** Bart Heldreth, Ph.D., Interim Director  
COSMETIC INGREDIENT REVIEW (CIR)

**FROM:** Beth A. Jonas, Ph.D.  
Industry Liaison to the CIR Expert Panel

**DATE:** August 17, 2017

**SUBJECT:** Updated Concentration of Use by FDA Product Category: *Hamamelis virginiana* (Witch Hazel)-Derived Ingredients

**Concentration of Use by FDA Product Category – *Hamamelis virginiana* (Witch Hazel)-Derived Ingredients\***

|   |   |
|---|---|
| Hamamelis Virginiana (Witch Hazel) Water                  | Hamamelis Virginiana (Witch Hazel) Extract      |
| Hamamelis Virginiana (Witch Hazel) Bark/Leaf Extract      | Hamamelis Virginiana (Witch Hazel) Flower Water |
| Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract | Hamamelis Virginiana (Witch Hazel) Leaf Extract |
| Hamamelis Virginiana (Witch Hazel) Bark/Twig Extract      | Hamamelis Virginiana (Witch Hazel) Leaf Water   |

| <b>Ingredient</b>   | <b>Product Category</b>   | <b>Maximum Concentration of Use</b> |
|---|---|-------------------------------------|
| Hamamelis Virginiana (Witch Hazel) Water                  | Eye lotions   | 1.4-6.6%                            |
| Hamamelis Virginiana (Witch Hazel) Water                  | Eye makeup removers   | 2%                                  |
| Hamamelis Virginiana (Witch Hazel) Water                  | Other eye makeup preparations                                     | 0.04%                               |
| Hamamelis Virginiana (Witch Hazel) Water                  | Colognes and toilet waters  | 0.00008%                            |
| Hamamelis Virginiana (Witch Hazel) Water                  | Shampoos (noncoloring)  | 2.5%                                |
| Hamamelis Virginiana (Witch Hazel) Water                  | Face powders  | 0.093%                              |
| Hamamelis Virginiana (Witch Hazel) Water                  | Foundations   | 4.3%                                |
| Hamamelis Virginiana (Witch Hazel) Water                  | Lipstick  | 0.1%                                |
| Hamamelis Virginiana (Witch Hazel) Water                  | Other manicuring preparations                                     | 4.3%                                |
| Hamamelis Virginiana (Witch Hazel) Water                  | Bath soaps and detergents   | 0.1-0.89%                           |
| Hamamelis Virginiana (Witch Hazel) Water                  | Deodorants<br>Not spray   | 5.2%                                |
| Hamamelis Virginiana (Witch Hazel) Water                  | Other personal cleanliness products                               | 1.5%                                |
| Hamamelis Virginiana (Witch Hazel) Water                  | Aftershave lotions  | 0.9-8%                              |
| Hamamelis Virginiana (Witch Hazel) Water                  | Shaving cream   | 0.0074-0.45%                        |
| Hamamelis Virginiana (Witch Hazel) Water                  | Skin cleansing (cold creams, cleansing lotions, liquids and pads) | 0.01-33.3%                          |
| Hamamelis Virginiana (Witch Hazel) Water                  | Face and neck products<br>Not spray                               | 0.00066-12.9%                       |
| Hamamelis Virginiana (Witch Hazel) Water                  | Body and hand products<br>Not spray<br>Spray                      | 0.1-4.3%<br>25.8%                   |
| Hamamelis Virginiana (Witch Hazel) Water                  | Paste masks and mud packs   | 0.00066-5%                          |
| Hamamelis Virginiana (Witch Hazel) Water                  | Skin fresheners   | 1%                                  |
| Hamamelis Virginiana (Witch Hazel) Water                  | Other skin care preparations                                      | 0.5-43%                             |
| Hamamelis Virginiana (Witch Hazel) Water                  | Suntan products<br>Pump spray                                     | 8.9%                                |
| Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract | Shaving cream   | 0.0035%                             |
| Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract | Skin cleansing (cold creams, cleansing lotions, liquids and pads) | 0.0005-0.072%                       |

|   |   |                      |
|---|---|----------------------|
| Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract | Face and neck products<br>Not spray                               | 0.004-4.3%           |
| Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract | Moisturizing products<br>Not spray                                | 0.072%               |
| Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract | Night products<br>Not spray                                       | 0.00005%             |
| Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract | Paste masks and mud packs   | 0.00005%             |
| Hamamelis Virginiana (Witch Hazel) Bark/Leaf/Twig Extract | Skin fresheners   | 0.18%                |
| Hamamelis Virginiana (Witch Hazel) Extract                | Bath oils, tablets and salts                                      | 0.000013-0.0001%     |
| Hamamelis Virginiana (Witch Hazel) Extract                | Other bath preparations   | 0.5%                 |
| Hamamelis Virginiana (Witch Hazel) Extract                | Eye lotions   | 0.1-35.8%            |
| Hamamelis Virginiana (Witch Hazel) Extract                | Other eye makeup preparations                                     | 35.8%                |
| Hamamelis Virginiana (Witch Hazel) Extract                | Colognes and toilet waters  | 0.00003-0.5%         |
| Hamamelis Virginiana (Witch Hazel) Extract                | Hair conditioners   | 0.3%                 |
| Hamamelis Virginiana (Witch Hazel) Extract                | Hair sprays<br>Pump spray   | 0.0001%              |
| Hamamelis Virginiana (Witch Hazel) Extract                | Face powders  | 0.05%                |
| Hamamelis Virginiana (Witch Hazel) Extract                | Foundations   | 0.003-0.05%          |
| Hamamelis Virginiana (Witch Hazel) Extract                | Lipstick  | 35.8%                |
| Hamamelis Virginiana (Witch Hazel) Extract                | Bath soaps and detergents   | 0.2%                 |
| Hamamelis Virginiana (Witch Hazel) Extract                | Deodorants<br>Not spray   | 0.0013%              |
| Hamamelis Virginiana (Witch Hazel) Extract                | Feminine hygiene deodorants                                       | 0.01%                |
| Hamamelis Virginiana (Witch Hazel) Extract                | Other personal cleanliness products                               | 0.01%                |
| Hamamelis Virginiana (Witch Hazel) Extract                | Aftershave lotions  | 0.0027-0.3%          |
| Hamamelis Virginiana (Witch Hazel) Extract                | Skin cleansing (cold creams, cleansing lotions, liquids and pads) | 0.0001-5%            |
| Hamamelis Virginiana (Witch Hazel) Extract                | Depilatories  | 0.000013%            |
| Hamamelis Virginiana (Witch Hazel) Extract                | Face and neck products<br>Not spray                               | 0.0001-1.8%          |
| Hamamelis Virginiana (Witch Hazel) Extract                | Body and hand products<br>Not spray<br>Spray                      | 0.0001-5%<br>0.03-5% |
| Hamamelis Virginiana (Witch Hazel) Extract                | Moisturizing products<br>Not spray                                | 0.0034%              |
| Hamamelis Virginiana (Witch Hazel) Extract                | Night products<br>Not spray                                       | 0.12%                |
| Hamamelis Virginiana (Witch Hazel) Extract                | Paste masks and mud packs   | 0.0034-0.1%          |
| Hamamelis Virginiana (Witch Hazel) Extract                | Skin fresheners   | 0.5-86%**            |
| Hamamelis Virginiana (Witch Hazel) Extract                | Other skin care preparations                                      | 1.1%                 |
| Hamamelis Virginiana (Witch Hazel) Extract                | Indoor tanning preparations                                       | 0.0013-6.1%          |
| Hamamelis Virginiana (Witch Hazel) Leaf                   | Hair conditioners   | 0.00042%             |

| Extract   |   |               |
|---|---|---------------|
| Hamamelis Virginiana (Witch Hazel) Leaf Extract | Shampoos (noncoloring)  | 0.00035%      |
| Hamamelis Virginiana (Witch Hazel) Leaf Extract | Tonics, dressings and other hair grooming aids                    | 0.00035%      |
| Hamamelis Virginiana (Witch Hazel) Leaf Extract | Deodorants<br>Not spray   | 0.00018%      |
| Hamamelis Virginiana (Witch Hazel) Leaf Extract | Skin cleansing (cold creams, cleansing lotions, liquids and pads) | 0.00035-0.01% |
| Hamamelis Virginiana (Witch Hazel) Leaf Extract | Face and neck products<br>Not spray                               | 0.0018%       |
| Hamamelis Virginiana (Witch Hazel) Leaf Extract | Body and hand products<br>Not spray                               | 0.011%        |
| Hamamelis Virginiana (Witch Hazel) Leaf Water   | Paste masks and mud packs   | 0.67-4.1%     |

\*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

\*\*86% Hamamelis Virginiana (Witch Hazel) Extract skin freshener is an OTC skin astringent.

Information collected in 2016-2017

Table prepared: February 1, 2017

Revised August 17, 2017: Hamamelis Virginiana (Witch Hazel) Water in non-spray deodorants changed from 5.2% from 6%; added \*\* for 86% Hamamelis Virginiana (Witch Hazel) Extract product; Hamamelis Virginiana (Witch Hazel) Leaf Water paste masks and mud packs concentration range changed from 4.1-5% to 0.67 to 4.1%