

## SUPPLEMENT

Aerosols

Alkoxylated Fatty Amides

Brown Algae

Polyaminopropyl Biguanide

Substantive Comments on Draft Final Reports

Acrylates Copolymers

Salicylic Acid and Salicylates

Vinylpyrrolidone Polymers

CIR EXPERT PANEL MEETING  
DECEMBER 3-4, 2018



Cosmetic  
Ingredient  
Review

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Memorandum

To: CIR Expert Panel Members and Liaisons  
From: Jinqiu Zhu, PhD, DABT, ERT, CIR Toxicologist  
Date: November 28, 2018  
Subject: Wave 3 Data on Aerosols

Enclosed is a letter and a study received November 21, 2018 from Ms. Alexandra Scranton, Director of Science and Research, Women's Voices for the Earth, presenting 5 comments on the Draft Revised Aerosols Precedents and Framework Document (Aerosols Document). This document is to be reviewed by the CIR Expert Panel (Panel) at the December 3<sup>rd</sup> - 4<sup>th</sup> 2018 meeting.

The comments are summarized briefly below, along with preliminary responses and other information that may be helpful for addressing the comments.

***Summary of comment #1: The boilerplate language continues to make broad assumptions and conclusions of safety about the inhalation of cosmetic products that are not supported by the data. The particle size data on deodorant sprays is actually coming from the very same sources as the hairspray data, and should be given equal weight and credibility and should be clearly stated as 50%.***

***Response:*** As a whole, the boilerplate language for the Cosmetic Use Section addresses deodorant sprays separately from other product types. If product(s) include spray(s) other than deodorants, the boilerplate language states, “In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm.” The “cosmetic sprays” therein do not include deodorants. In comparison, if it is known that a deodorant formulation is a spray, we add “there is some evidence indicating that deodorant spray products can release substantially larger fractions of particles having aerodynamic equivalent diameters in the range considered to be respirable.<sup>1</sup> However, data are not sufficient to determine the extent of lung exposures that result from the use of deodorant sprays, compared to other cosmetic sprays. Particle/droplet size data under consumer use conditions are rarely needed when assessing the inhalation safety of an ingredient in a spray cosmetic product. A tiered approach to the exposure assessment of spray products requires actual exposure measurements and more refined modelling to determine the realistic estimates of respirable particle fractions released from aerosol sprays.<sup>2,3,,</sup>

As discussed in the Precedents document, although a conservative estimation indicating up to 50% of the particle size distribution released from propellant deodorant sprays consist of respirable particles, there are numerous factors that need to be considered when conducting an inhalation risk assessment, such as product parameters of formulation, nozzle size, type of propellant gas and pressure stage, as well as the exposure parameters, including spray time, frequency, spray direction, the room size, the temperature, ventilation rate, and the breathing rate, etc. Therefore, a tiered approach to inhalation safety assessment is always recommended to estimate the respirable droplets/particles that actually deposit in the pulmonary region.

As the Commenter indicates, the particle size or particle size distribution data are not available for the some types of cosmetic sprays (i.e., airbrush makeup, sunless tanning, spray-on hair color, spray lotion, spray on nail polish, and lacewig adhesive spray). In addition, data regarding exposure and device parameters, as well as the actual measurements under in-use conditions of these sprays, are lacking. Therefore, these types of sprays are not specifically discussed in the Precedents document, which mainly reflects the current state of the knowledge on cosmetic pump and propellant sprays.

Accordingly, the Panel is being asked to determine: 1) whether the information on hair sprays can be included as a “worst-case” scenario, and therefore always included in the boilerplate language to represent cosmetic sprays other than deodorant sprays? and 2) is additional boilerplate language necessary to address the issue that we currently lack the data on some types of sprays, and therefore cannot characterize the inhalation exposure to these spray products?

Principle considerations for the risk assessment of sprayed consumer products are summarized in the revised Precedents document. Cosmetic sprays include different ingredients and have different exposure patterns. In situations when relevant parameters are not available to conduct a robust inhalation risk assessment, industry need disclose information to ensure the safety of cosmetic spray and powder products, including information characterizing the size distributions of the particles and droplets emanating from products, when used as intended, as well as factors such as the identities and concentrations of the ingredients in the cosmetic formulations. Specifically, for those new types of cosmetic sprays, industry needs to perform an empirical study to characterize the particle size distributions released from an adequate number of representative cosmetic spray products using appropriate tools and methods.

Accordingly, the Panel is being asked to determine, in a situation when the relevant information is not provided by industry, data would then be considered to be insufficient to determine the safety of an ingredient by inhalation during the application of cosmetic sprays?

***Summary of comment #2: “Cosmetic sprays” incorporate numerous different products not considered by this analysis. In addition to hair sprays and deodorant sprays, cosmetic of many kinds can come in spray form and potentially be inhaled.***

**The Aerosols boilerplate language refers generally to “cosmetic sprays” and comes to assumed conclusions of safety largely based on the following assumption: “In practice, exposure to an ingredient during the application of cosmetic sprays will be very low, due to low use quantities and very short exposure times.”**

**There is no available data on these types of cosmetic sprays that could corroborate this assumption is also true for these products and their potential exposures.**

**Response:** As discussed above, other types of cosmetic sprays, e.g., airbrush makeup, sunless tanning and spray-on hair color, are not specifically discussed in the Precedents document due to a lack of particle size distribution data and/or exposure parameters under simulated use conditions. On the other hand, a recent study indicates that when a tiered approach is applied to inhalation risk assessment, the exposure to an ingredient in a spray formulation is dramatically decreased (e.g., exposure to aluminum chlorohydrate in aerosol form, see the details in Response to comment #3 below). Based on the current weight of evidence, the boiler plate language addresses deodorant sprays separately from other product types and states that “In practice, exposure to an ingredient during the application of cosmetic sprays will be very low, due to low use quantities and very short exposure times.”

Accordingly, the Panel is being asked to determine whether such a sentence should be included.

***Summary of comment #3: The boilerplate language regarding exposure to cosmetic powders has not been updated, and still reflects assumptions of safety based solely on talc data from 1979, which is not only outdated but is likely not reflective of all cosmetic exposures.***

**Response:** Industry recently submitted the particle size distribution data for aerosol hair spray and aerosol deodorant/antiperspirant, but the data regarding the concentration of airborne particles released from cosmetic powder products have not been updated yet. However, CIR also considers information from other sources and thus performed a literature search in data discovery, regarding the inhalation exposure to ingredients in powder form dispersed with or without the spray formulation.

One review paper, “Principles for the Safety Evaluation of Cosmetic Powder”, provides usage amounts data for loose powder foundation/face powder, ranging from 73 to 85 mg/day.<sup>4</sup> In 2015, the Danish Environmental Protection Agency (EPA) reported an estimated exposure to silica in face powder at 0.9 µg/kg/day for a 60 kg person.<sup>5</sup> Note that such estimation is based on a conservative estimate of face powder usage at 0.51 g (510 mg) per application per day as well as the assumption that 1% of face powder is respirable.<sup>5,6</sup> Furthermore, if the use amount of face powder from the published paper, i.e., up to 85 mg/day,<sup>4</sup> is used in such calculation, the estimated exposure to face powder would be 6 times lower

than 0.9 µg/kg/day (0.15 µg/kg/day vs. 0.9 µg/kg/day). These data were incorporated to the revised Precedents documents (see administrative book, pdf page 102).

In addition, a 2018 study on the assessment of inhalation exposure to aluminum chlorhydrate powder, which is dispersed within a spray formulation, was added to the Precedents document (see Administrative book, pdf page 102).<sup>7</sup> In this study, a tiered approach for the evaluation of inhalation safety was applied, by mimicking realistic consumer use conditions and incorporating particle/droplet size data. Internal exposure to aluminum chlorhydrate was first refined by a two-box exposure model, and further calculated using the Multiple Path Particle Deposition model. The total systemic exposure via inhalation was found to be less than 0.5 µg per application (less than 0.0084 µg/kg/application for a 60 kg person). In the revised Precedents document, we conducted a calculation based on a conservative estimate of the frequency of use at two applications per day, yielding an exposure estimate to aluminum chlorhydrate from aerosol sprays at 0.168 µg/kg/day for a 60 kg person.<sup>8</sup>

Therefore, the revised Precedents document **does** include updated data related to inhalation exposure of ingredients in powder form. Comparing the exposure data from the Danish EPA report (0.9 µg/kg/day to silica in face powder) and from the recently published paper (0.0084 µg/kg/application or 0.168 µg/kg/day to aluminum chlorhydrate powder dispersed with the aerosol spray formulation), the exposures to a loose face powder or body dusting product ranges from 0.1 to 1.05 µg/kg/day for infants or adults still represent a conservative estimation for the current state of cosmetic powder use. In addition, recent studies indicated that most of the mass (85% to 93%) of inhaled airborne particles released from cosmetic powders is deposited in the head airways, not the pulmonary region.<sup>9,10</sup> Inhalation exposure to other ingredients in cosmetic powder products would be calculated and incorporated into the document once the relevant respirable particles concentration data are available (the data will be either discovered in the literature or provided by Industry).

The Commenter submitted a “paper” on particle size distribution of cosmetic mineral makeup powders, “Morphologi G3: Understanding Mineral-based Make-up using Size, Shape and Intensity Measurements”,<sup>11</sup> to demonstrate that more accurate technology is now available to measure the concentrations of respirable particles from cosmetic powders. However, the “paper” itself is not a peer-reviewed article, but more likely an advertisement released by the equipment manufacturer. Three types of mineral-based powder make-up products were analyzed but the sample size for each type of product was not known (seems that only one sample was analyzed for each type). Thus, the data included in this “paper” warrant further validation and cannot be incorporated into the Precedents document.

***Summary of comment #4: The citations for several of the newly included calculation examples do not correspond to the relevant papers and should be corrected:***

- A citation is needed for the estimate of 1.43 g/day used of propellant deodorant spray
- The data regarding the use amount of loose face powder (73.1 to 85 mg) can not be found in the cited papers (Ficheux et al., 2015 and Loret et al., 2008)
- The SCCS's notes of guidance for the testing of cosmetic ingredients and their safety evaluation (7th Revision) does not include an estimated use of face powder at 510 mg/day

***Response:***

1. The estimate use of 1.43 g/day of propellant deodorant spray is from the SCCS Notes of Guidance, 2010 (the latest 9<sup>th</sup> version was updated in 2016),<sup>6</sup> was also cited in Rothe et al., 2011.<sup>12</sup> See the highlight in Table 1.

Table 1 Estimated daily exposure levels for different cosmetic product types.

Product type	Estimated daily amount applied	Relative amount applied (mg/kg bw/d)	Retention factor	Calculated daily exposure (g/d)	Calculated relative daily exposure (mg/kg bw/d)
<b>Bathing, showering</b>					
Shower gel	18.67 g	279.20	0.01	0.19	2.79
Hand wash soap	20.00 g	-	0.01	0.20	3.33

<b>Hair care</b>					
Shampoo	10.46 g	150.49	0.01	0.11	1.51
Hair conditioner	3.92 g	-	0.01	0.04	0.60
Hair styling products	4.00 g	57.40	0.1	0.40	5.74
Semi-permanent hair dyes (and lotions)	35 ml (per application)	-	0.1	Not calculated	-
Oxidative/permanent hair dyes	100 ml (per application)	-	0.1	Not calculated	-

<b>Skin care</b>					
Body lotion	7.82 g	123.20	1.0	7.82	123.20
Face cream	1.54 g	24.14	1.0	1.54	24.14
Hand cream	2.16 g	32.70	1.0	2.16	32.70

<b>Make-up</b>					
Liquid foundation	0.51 g	7.90	1.0	0.51	7.90
Make-up remover	5.00 g	-	0.1	0.50	8.33
Eye shadow	0.02 g	-	1.0	0.02	0.33
Mascara	0.025 g	-	1.0	0.025	0.42
Eyeliner	0.005 g	-	1.0	0.005	0.08
Lipstick, lip salve	0.057 g	0.90	1.0	0.057	0.90

<b>Deodorant</b>					
Deodorant non-spray	1.50 g	22.08	1.0	1.50	22.08
Deodorant aerosol spray (ethanol-based)	1.43 g	20.63	1.0	1.43	20.63
Deodorant spray	0.69 g	10.00	1.0	0.69	10.00

(Note: Table in SCCS Note and Guidance, 2016<sup>6</sup>

Available at [http://ec.europa.eu/health/scientific\\_committees/consumer\\_safety/docs/sccts\\_o\\_190.pdf](http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccts_o_190.pdf))

2. The updated use amounts of loose powder foundation / face powder (73 - 85 mg) are from a review paper, entitled “Principles for the Safety Evaluation of Cosmetic Powders,”<sup>4</sup> which has also been submitted for the Panel’s review (see the highlights in Table 2). The frequency of use data of various cosmetic products were provided in Ficheux et al 2015,<sup>13</sup> while the use amounts data were provided in Ficheux et al 2016.<sup>8</sup> According to the data summary in the table of the review paper, the use amounts data of loose powder foundation / face powder (73 - 85 mg) are supported by four original articles.<sup>8,14-16</sup> However, after carefully checking the data in the individual paper, one citation that does not include the use data of face power will be deleted from the Precedent documents.<sup>16</sup>

Table 2 Literature examples of use frequency, usage amounts and respirable fraction for cosmetic powders.

Product type	Parameter	Input mean values	Reference
Dry shampoo	Frequency/day	0.23 (pregnant women)	Ficheux et al., 2015
Eye shadow		0.72	
Compact powder foundation		0.71	
Loose powder foundation		0.74	
Blush		0.73	
Dry shampoo	Amount/application	2.4 g	Ficheux et al., 2016
Eye shadow		9.1 mg	

Compact powder foundation		59.6 mg	
Loose powder foundation		73.1 mg	
Blush		13.1 mg	
Eye shadow	Frequency/day	0.40 to 0.78	Cosmetic, Toiletry and Fragrance Association (CTFA, 1983)
Blusher and rouge		0.55 to 1.24	
Face powder		0.33 to 0.67	
Blusher and rouge	Amount/application	11 mg 85 mg	Loretz et al., 2008
Face powder		1%	
Eye shadow	Frequency/day	1.2	
Eye shadow	Amount/application	30 mg	Danish EPA, 2015
Face powder	Respirable fraction	1%	
Baby powder	Amount/application	107 mg	Moon et al., 2011

Note: Table in Steiling et al, 2018<sup>4</sup>

3. The Danish Environmental Protection Agency (EPA) reported an inhalation exposure to silica in face powder at 0.9 µg/kg/day for a 60 kg person in 2015.<sup>5</sup> The Danish EPA stated in their document that the estimated applied amount of face powder is 0.51 g/day (510 mg/day) and the exposed area 565 cm<sup>2</sup> (50% of the area of the female head). See the highlights in Table 3.

The SCCS's Notes of Guidance (8<sup>th</sup> Revision 2012, 9<sup>th</sup> version updated in 2016)<sup>6</sup> was cited by the Danish EPA as the data source therein.<sup>5</sup> However, in SCCS Notes of Guidance, the cosmetic type that matches the two parameters that quoted by the Danish EPA, i.e., the use amount of 0.51 g/day and the exposure area of 565 cm<sup>2</sup>, refers to liquid foundation (face powder is not listed as a cosmetic type in SCCS Notes of Guidance, as shown in Table 1 above). While liquid foundation and face powder do not belong to the same category according to the FDA VCRP database, the Danish EPA seemed to use liquid foundation use data at 0.51 g/day (510 mg/day) to represent a worse-case scenario for the exposure to face powder; the actual use amounts of face powder reported in the literature range from 73-85 mg (see Response #2 and Table 2 above for the details).

Table 3 Exposure to silica in face powder.

No.	Product	NM	Exp. scenario (application/use) (product volume used) (NM concentration in product)	Target group	Nanomaterial Exposure			
						Dermal	Inhalation	Eye
9.	Face Powder	Silica	Application in face using brush 0.51 g powder containing 100 mg nano-silica/g (10%)	Teenagers	0.43 mg/day 0.008 mg/kg/day	0.09 mg/cm <sup>2</sup> 51 mg/day 0.90 mg/kg/day	0.26 mg/m <sup>3</sup> 0.051 mg/day 0.0009 mg/kg/day 10,000 particles (20 nm)/cm <sup>3</sup> 2 x 10 <sup>9</sup> particles (20 nm)/day	0.00009 mg/cm <sup>2</sup> 0.006 mg/day 0.00001 mg/kg/day

Note: Table in the Danish EPA's report, 2015<sup>5</sup> Available at <https://www2.mst.dk/Udgiv/publications/2015/07/978-87-93352-48-3.pdf> (page 45-46)

**Comment 5:** While there is more nuanced discussion in the background section of the Precedent document, the actual boilerplate language includes the following sentence: “Particle/droplet size data under consumer use conditions are rarely needed when assessing the inhalation safety of an ingredient in a spray cosmetic product.” This statement appears either to contradict a major tenet of inhalation toxicology, (i.e. that particle size is indeed a significant factor) or to imply that the CIR is simply uninterested in investigating particle size data when they assess an ingredient for inhalation safety.

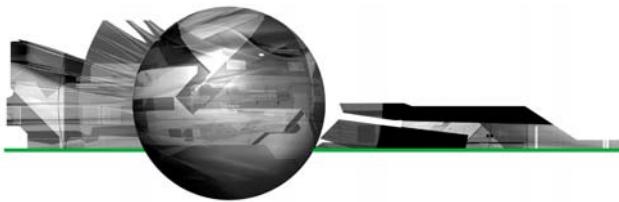
**Response:** The CIR SSC recommends the boiler plate language should reflect less reliance on particle size and more emphasis on exposure levels from spray cosmetic products by the inhalation route. While particle/droplet size is an important parameter, other exposure factors are key in assessing inhalation safety. A tiered approach is outlined in the revised Precedents document. As shown in one study, when a tiered approach is applied, the total systemic exposure to aluminum chlorohydrate via inhalation is found to be less than 0.5 µg per application.<sup>7</sup> For comparison, exposure to 2 mg/m<sup>3</sup> (which is the concentration a worker can be exposed to day after day for a working lifetime without adverse health effects, according to the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) for one working day (female breathing rate light activity 9.12 m<sup>3</sup>/day)),<sup>17</sup> would result in an exposure of 18.3 mg. There are 4 orders of magnitude difference between the two values.

Accordingly, the Panel is being asked to determine whether the sentence regarding particle/droplet size should be included.

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## Morphologi G3: Understanding Mineral-based Make-up using Size, Shape and Intensity Measurements

### Introduction

Mineral-based powder make-up is an increasingly popular consumer care product where particles of specific size and shape are blended to obtain a product that, in the end, aims to perfectly hide the fact that it is made of discrete particles. The light dispersing properties of the particles are highly influenced by the factors mentioned above and therefore it may be useful in R&D or Quality assurance applications to understand such properties.

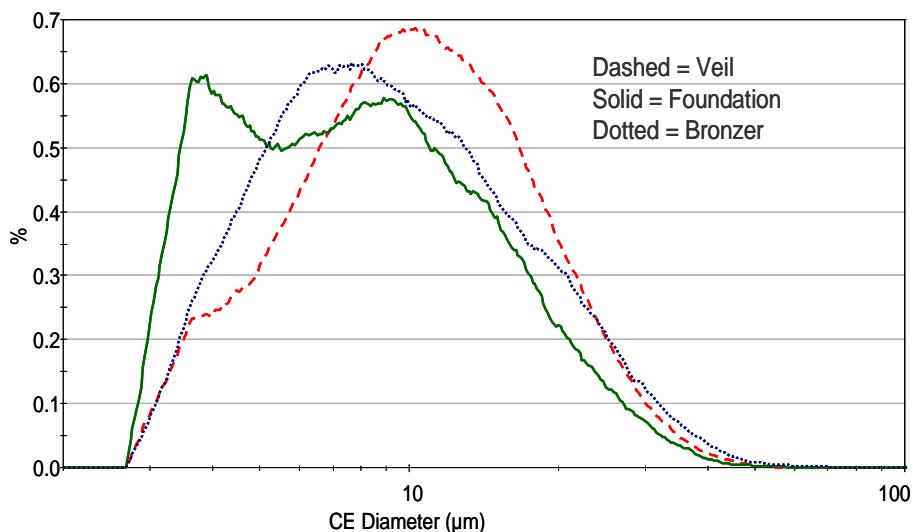
In this application note we explore the particles size and shape distribution of three commercially-available mineral-based powders.

### Materials and Method

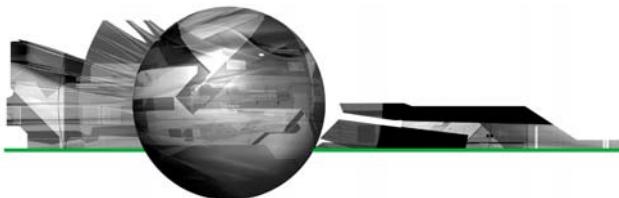
Mineral-based powder make-up was purchased from a large surface retailer. A sample of the powder was retrieved from the top of the container and consequently corresponds to what might be used in a first application from each bottle. We did not explore segregation in these bottles. Two of the products are from the same product line, but aim to achieve different functions. The first product is an ivory-tinted foundation formulated to provide coverage, tint and diffuse light, and the second is a bronzer. Bronzers typically contain coated mica and aim to add a darker reflective finish. Finally, the third product is a mineral veil from a different brand: the veil is a sheer product that aims to absorb oil and

minimizes the appearance of pores by diffusing light.

The Morphologi G3S (Figure 1) was used to disperse and measure the dry particles according to a Standard Operating Procedure (SOP) that contained all of the software and hardware settings. For the dispersion a pressure of 0.8 bar was applied for 10 ms and the sample was allowed to settle for 30 seconds. These settings were selected since they generated a dispersion where most particles were individually separated, with very few aggregates, without causing particle breakage. The sample was analyzed with the 10x magnification and more than 10,000 particle images were collected per product with a total data acquisition time of approximately 15 minutes each.



**Figure 1:** The Morphologi G3S and the overlay of the number-based CED distributions of three mineral-based make-up samples



## Results and Discussion

Particle size in the powder affects the final make up appearance where extremes lead to a poor finish. When the particles are too large a powdery look is observed and when the particles are too small there is an insufficient masking effect.

Figure 1 shows the overlay of the number-based particle size distribution of the three samples in terms of Circular Equivalent Diameter (CED). The CED was selected as the measurement of size because it is convenient for comparison with traditional particle sizing techniques, such as laser diffraction, which assumes spherical particles.

For this application a number-based distribution better represents particle size since smaller particles are important; indeed each particle, regardless of its size, has the same contribution to the distribution in a number-based approach.

Figure 1 shows there is a clear bimodal size distribution in the foundation product and the veil is generally made of larger particles.

Images of every particle analyzed are retained by the system and can be used to visually inspect the products, thereby providing a qualitative analysis of the sample. Figure 2 shows some example images of large and medium sized particles from the three products. In the veil product, the

largest particle is obviously an aggregate of plates, while the third largest is an aggregate of dark pseudo-spherical particles. The two other products do not show such aggregates among their largest particles. In all cases, there are plate-like and pseudo spherical-like particles in the medium size group. Similar particle size, shape and intensity (opacity) are observed in this table for the three samples and a statistical analysis of a larger number of particles is necessary to understand the bulk differences between the samples.

The ability to measure and compare large numbers of particles in a powder sample is the strength of automated image analysis; by acquiring images

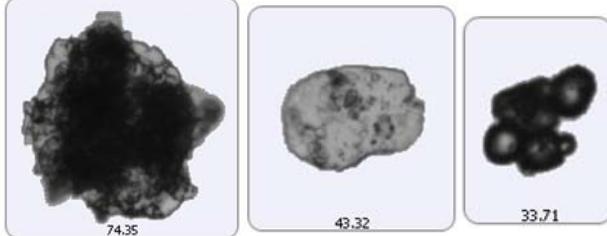
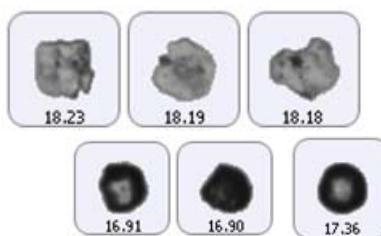
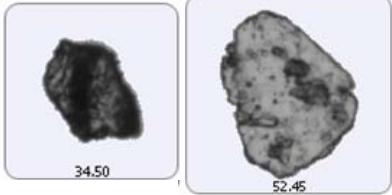
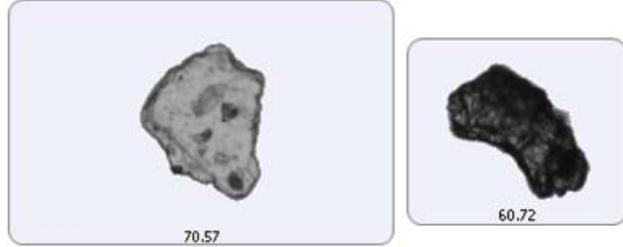
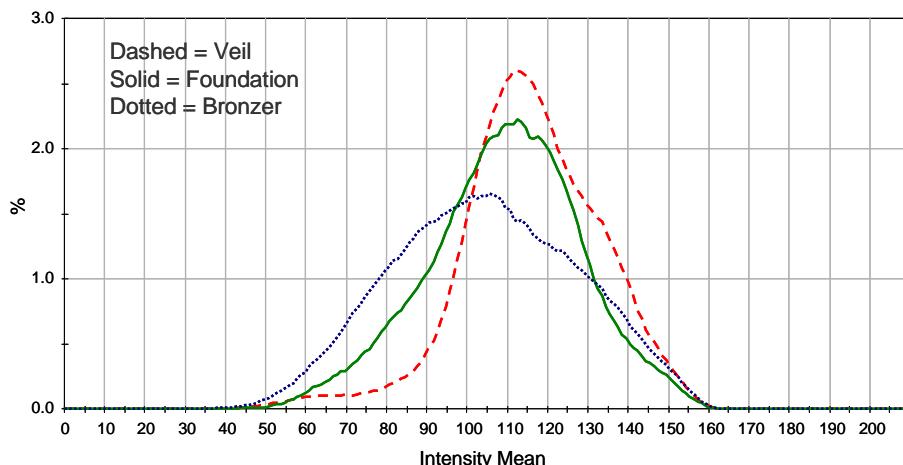
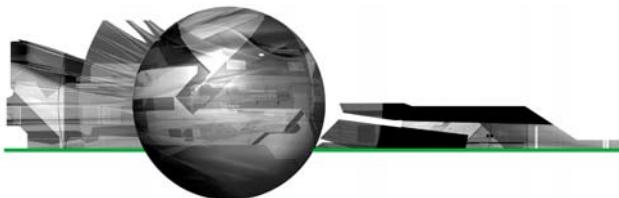
	Largest	Medium sized
Veil	 74.35      43.32      33.71	
Foundation		
Bronzer		

Figure 2: Images of particles from the three samples



**Figure 3:** Intensity distribution for the three mineral make-up samples.

from thousands to tens of thousands of particles, it is possible to obtain a more reliable characterization than is typically obtained with manual microscopy, which is labor intensive and may be highly influenced by the operator's skills.

Particle shape is very important in make-up because of its effect on light reflection. For example, plate-like crystals create a pearlescent effect where the size of the plates determines the level of sparkle: Small plates give a more opaque smooth finish, while larger plates add a brilliant spark.

The mean intensity in a diascopic measurement is an indication of the transparency of the particles. Considering the finish requirements of the three samples, it is not surprising that very different mean intensity profiles were measured. Figure 3 shows a overlay of the mean intensity distributions of the particles in the three samples. These distributions correspond well with the product properties, where the particles in the veil are more transparent and the particles in the bronzer are the darkest.

It is also possible to use multiple parameters to compare samples

and provide classification statistics. It is important to select characteristics that are related to the performance of the product and for this case, we selected the CED and the mean intensity.

Classes were set up as follows:

Large Lighter: CED>10µm and Intensity mean >130 grey scale.

Large Darker: CED>10µm and Intensity mean <130 grey scale.

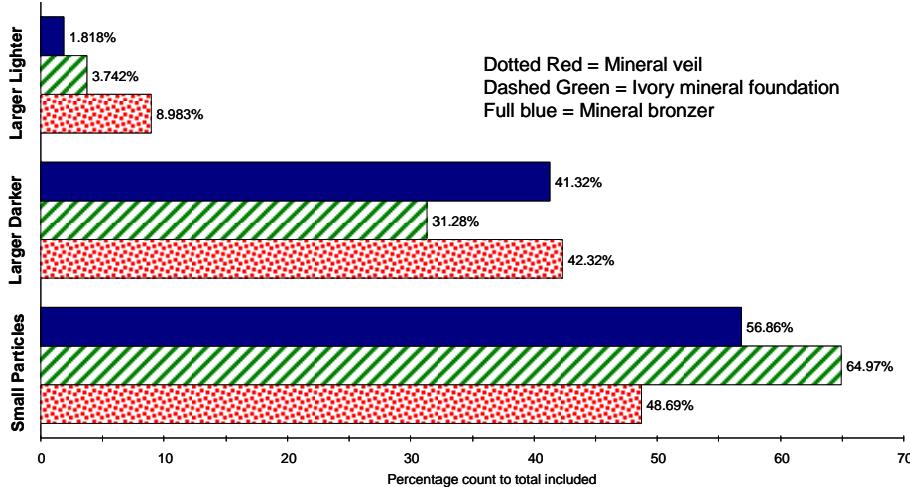
Small Particles: CED<10 µm.

Figure 4 shows the proportions of particles in each of the three classes. As expected, the veil product contains a greater proportion of large lighter particles, which are typically used to diffuse light while not imparting any pigmentation. The bronzer shows a different trend, with a greater proportion of dark particles in the large size fraction, but also more small particles than the veil, probably to add spark to the bronzed look it is meant to achieve.

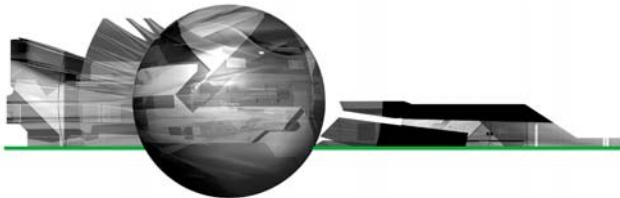
Obviously, this type of analysis is useful in Quality Assurance applications, where understanding the proportions of various types of particles is key to ensuring the desired functional properties.

## Conclusion

Particle imaging is a discipline that was once labor-intensive and highly subjective because it was performed manually. The development of automated particle imaging instruments equipped with integrated computer-controlled dispersion, advanced image processing and statistical analysis tools, such as the Morphologi G3S, have taken this informative technique to a new level



**Figure 4:** bar chart showing the results of the Classification



where the quantitative data can be used in formulation development, for quality control and for reverse engineering. We focused this application note on characteristics of the larger particles, but higher magnification measurements would provide similar information about the smaller particles.

The Morphologi G3S instrument is flexible and allows for a very broad range of measurements to be made, which can be designed to verify properties of specific interest.

**Malvern Instruments Ltd**

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# WOMEN'S VOICES FOR THE EARTH

OUR HEALTH. OUR FUTURE. TOXIC FREE.

November 21, 2018

To the CIR,

I am writing to provide comments on the revised Aerosol CIR Precedents document. I greatly appreciate the extensive discussions and considerations of my previous comments on this issue. However, I remain concerned that

- 1) the boilerplate language continues to make broad assumptions and conclusions of safety about the inhalation of cosmetic products that are not supported by the data.
  - 2) the narrow focus on just hairsprays and aerosol deodorants is severely limiting, given the numerous other cosmetic products that come in spray form, which may have considerably different ingredients, exposure levels and use frequencies.
  - 3) the boilerplate language regarding exposure to cosmetic powders has not been updated, and still reflects assumptions of safety based solely on talc data from 1979, which is not only outdated but is likely not reflective of all cosmetic exposures.
  - 4) the citations for several of the newly included calculation examples do not correspond to the relevant papers and should be corrected and,
  - 5) while there is more nuanced discussion in the background section of the Precedent document, the actual boilerplate language includes the following sentence:  
*"Particle/droplet size data under consumer use conditions are rarely needed when assessing the inhalation safety of an ingredient in a spray cosmetic product."*
- I believe this assertion, which could be included in isolation in a safety assessment, reflects poorly on the scientific understanding of the CIR.

- 1) The boilerplate language continues to make broad assumptions and conclusions of safety about the inhalation of cosmetic products that are not supported by the data.**

At the very beginning of the Cosmetics Use Section of the boilerplate language it states:

*"In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm [IF PRODUCT(S) MAY INCLUDE BOTH PROPELLANT AND PUMP SPRAYS, ADD: , with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump sprays]. (Rothe et al 2011, Bremmer et al 2006, Rothe 2011, Johnsen 2004).<sup>1,12,17,46</sup> Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount. Rothe et al 2011, Bremmer et al 2006).<sup>1,12</sup> [IF PRODUCT(S) INCLUDE DEODORANT SPRAY(S), ADD:*

*There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable (Bremmer et al 2006).<sup>12</sup>*

The data currently available to the CIR includes particle size distributions solely for hairsprays and deodorant sprays. (This includes the ConExpo Model data (Bremmer 2006) as well as the new data submitted to the CIR by industry for this document.) Hairsprays have been generally found to have 95% of particles  $>10 \mu\text{m}$ , while deodorant sprays have been found to have only 50% of particles  $>10 \mu\text{m}$ . The boilerplate language, however, inaccurately generalizes the hairspray data and applies it to all “cosmetic sprays”. (There is simply no data on any other cosmetic sprays other than deodorant sprays to corroborate this assumption.)

Then later, as if in contrast, the document states there is “*some evidence indicating that deodorant spray products can release substantially larger fractions...*” The particle size data on deodorant sprays is actually coming from the very same sources as the hairspray data, and should be given equal weight and credibility and should be clearly stated as 50%.

Given that, it is illogical to conclude “*Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount).*” Again, this statement is conflating conclusions from data on hairsprays with all cosmetic sprays. The term “cosmetic sprays” clearly includes deodorant sprays, and for deodorant sprays it is inaccurate to state that “most” particles would not be respirable, when the data tells us that at least half of particles would be respirable.

- 2) **“Cosmetic sprays” incorporate numerous different products not considered by this analysis.**  
In addition to hair sprays and deodorant sprays, cosmetic of many kinds can come in spray form and potentially be inhaled. These cosmetic sprays include different ingredients and have different exposure patterns than either hairsprays or deodorant sprays. Specifically, cosmetic products include:

**Airbrush makeup** (this is done at home as well as professionally)

If you are unfamiliar with this cosmetic product, I highly recommend the following video tutorial of how to apply airbrush makeup at home:

<https://www.youtube.com/watch?v=yBPry8aj3oY>

You will see in this video that the airbrush makeup is sprayed directly to the face, and full application of airbrush foundation takes about four minutes of near-continuous spraying. (Learning to use this tool – would certainly involve longer application times, and additional layers of airbrush rouge, eye shadow etc can also be sprayed in addition, further increasing the exposure time.) The exposure time to this cosmetic spray is clearly significantly longer than exposures to hair spray or deodorant spray. Particle sizes for airbrush makeup are not currently available, but particles are likely to be quite small as larger particles would clog the airbrush.

### **Sunless tanning**

Similarly, sunless tanning products are commonly applied in spray form to get an even overall look. In addition to spraying directly at the face, spray tans can also be applied over the entire body. Full body application of spray tans can take up to 15-20 minutes of continuous spraying. Particle sizes for sunless tanning cosmetic sprays are currently not available.

### **Spray-on hair color**

These products are very popular currently, especially among children and teens, with products affording color that lasts just one day, to more lasting colors. To get a sense of potential amount of usage, a single can of "Colorista 1-day-spray" contains 57 grams of product.

According to the manufacturer's website

*"If you're looking for allover color, you may need to use more than one can."*

<https://www.lorealparisusa.com/beauty-magazine/hair-color/hair-color-trends/how-to-use-colorista-1-day-sprays.aspx>

Other cosmetic sprays not addressed in the boilerplate language include:

**Spray lotion** (including both sunblock aerosol sprays and moisturizing lotion sprays)

**Spray on nail polish** (and airbrush nail polish)

**Lacewig adhesive spray** (and hair glue remover sprays)

The Aerosols boilerplate language refers generally to "cosmetic sprays" and comes to assumed conclusions of safety largely based on the following assumption:

*"In practice, exposure to an ingredient during the application of cosmetic sprays will be very low, due to low use quantities and very short exposure times."*

There is no available data on these types of cosmetic sprays that could corroborate this assumption is also true for these products and their potential exposures.

- 3) **The boilerplate language regarding exposure to cosmetic powders has not been updated, and still reflects assumptions of safety based solely on talc data from 1979.**

With respect to inhalation hazards of cosmetic powders, the boilerplate language states:

*"Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace. (Aylott et al 1979, Russell et al 1979, CIR SSC 2015).<sup>38-40]</sup>*

In my previous comments I raised a concern that the assurances of safety of inhalation of cosmetic powders should be based on more recent data than what was available in 1979, using outdated technology. However, despite what appears from the transcripts to be agreement among the CIR members that there should be newer data, no new data on particle size distribution of powders has been included in the latest revision.

The claim that inhalation exposures to respirable particles are 400-1000 fold less than regulatory guidelines is derived from calculations made in 2015 by the CIR SSC based on reported airborne concentrations of respirable particles from the use of talc powder which come from the 1979 data (Aylott et al 1979, Russell et al 1979). This is inappropriate, when the issue has been raised and discussed that better and more accurate technology is now available to measure airborne concentrations of respirable particles from cosmetic powders.

For example, the Malvern company (which makes one of the most popular particle sizers - the Mastersizer 3000) published a paper on particle size distribution of cosmetic “mineral makeup” powders. The paper entitled “Morphologi G3: Understanding Mineral-based Make-up using Size, Shape and Intensity Measurements” is available at:

<https://kdsi.ru/upload/iblock/967/967d6aaf3337ef0e88bac0fd599a881b.pdf> They found that for three commercially available mineral make-up products, a veil, a foundation and a bronze, 48 – 66% of the particles were smaller than 10 microns in diameter. They explain that particle size is specifically engineered to support the function of the powder. *“Particle size in the powder affects the final make up appearance where extremes lead to a poor finish. When the particles are too large a powdery look is observed and when the particles are too small there is an insufficient masking effect.”* It appears that manufacturers, if asked, should be able to provide particle size information about their cosmetic powders currently on the market, as many products will be designed with particle size specifications in mind.

Also, reflecting the advances in technology, the paper states:

*“Particle imaging is a discipline that was once labor-intensive and highly subjective because it was performed manually. The development of automated particle imaging instruments equipped with integrated computer-controlled dispersion, advanced image processing and statistical analysis tools, such as the Morphologi G3S, have taken this informative technique to a new level.”*

The CIR should simply have the best and most recent data at its disposal to ensure the safety of inhalation of cosmetic powders. The discussion and analysis of cosmetic powders should also go beyond talc which is currently the only example being considered by the CIR.

#### 4) Examples of incorrect citations in the Aerosols Precedent document

The document includes the following calculation:

*“For example, conservative estimates indicate that inhalation exposures for once-a-day application of a pump hair spray, propellant hair spray or propellant deodorant spray containing 2% of an ingredient would be no more than 1.5, 4.7, and 6.8 µg/kg/day, respectively.<sup>35,36</sup> These estimates were based on the following conservative assumptions:*

- All of the spray enters the breathing zone (i.e., 100% is available for inhalation)
- Two-box exposure model: the droplets/particles distribute in 1000 L in the first 2 minutes, and distribute 10,000 L in the next 18 minutes
- 25% of the inhaled droplets/particles are exhaled
- Breathing rate: 10 L/minute

- *Body weight: 60 kg*
- *Amount of product used: 15.6, 9.89 and 1.43 g/day pump-hair, propellant-hair, and propellant deodorant spray, respectively*<sup>37</sup>
- *Respirable fraction: 1%, 5%, 50% for pump-hair, propellant-hair and deodorant spray, Respectively"*

I was particularly interested in the citation #37, cited as the source for "Amount of product used: 15.6, 9.89 and 1.43 g/day pump-hair, propellant-hair, and propellant deodorant spray, respectively"<sup>37</sup>

However, citation #37 is the following paper: Loretz L, Api AM, Barraj L, Burdick J, Davis de A, Dressler W, Gilberti E, Jarrett G, Mann S, LauriePan YH, Re T, Renskers K, Scrafford C, and Vater S. Exposure data for personal care products: hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant. Food Chem Toxicol. 2006;44(12):2008-2018. PM:16920244

While this paper appears to be a source for hairspray data this paper does not measure amount of product used for propellant deodorant spray, it only measures use of solid antiperspirant. Thus, a citation is needed for the estimate of 1.43 g/day used of propellant deodorant spray.

Similarly, the document later states:

*"Literature reports of use amount for one-a-day application of a loose face powder range from 73.1 to 85 mg.<sup>41,42</sup> Assuming 1% of a loose face powder is respirable yields an estimated exposure no more than 0.9 µg/kg/day for a 60 kg person,<sup>43</sup> based on a conservative estimate use of face powder at 510 mg per application per day.<sup>44"</sup>*

However, citation 41 is Ficheux, A. S., Wesolek, N, Chevillotte, G, and Roudot, AC. Consumption of cosmetic products by the French population. First part: frequency data. Food Chem. Toxicol. 2015;78:159-169. PM:25680505. This paper reports on a survey of frequency of use of various cosmetic products (ie. how often cosmetics get used) and does not include any data on amount of use for any cosmetic products.

Citation 42 is Loretz, L. J., Api, AM, Babcock, L, Barraj, LM, Burdick, J, Cater, KC, Jarrett, G, Mann, S, Pan, YH, Re, TA, Renskers, KJ, and Scrafford, CG. Exposure data for cosmetic products: facial cleanser, hair conditioner, and eye shadow. Food Chem. Toxicol. 2008;46(5):1516-1524. PM:18243463. This paper only estimates usage of facial cleanser, hair conditioner and eye shadow – and does not discuss loose face powder.

Citation 44 is Scientific Committee on Consumer Safety (SCCS). The SCCS's notes of guidance for the testing of cosmetic ingredients and their safety evaluation (7th Revision).  
2010. [http://ec.europa.eu/health/scientific\\_committees/consumer\\_safety/docs/sccs\\_s\\_004.pdf](http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_004.pdf). This is a long report, but I was unable to find any data here corresponding to an estimated use of face powder either. Correct citations in these sections would be appreciated.

5) Lastly, I caution the CIR from including the following language in the boilerplate:

***"Particle/droplet size data under consumer use conditions are rarely needed when assessing the inhalation safety of an ingredient in a spray cosmetic product."***

This statement appears either to contradict a major tenet of inhalation toxicology, (i.e. that particle size is indeed a significant factor) or to imply that the CIR is simply uninterested in investigating particle size data when they assess an ingredient for inhalation safety.

Thank you for your consideration of these comments.

Sincerely,

A handwritten signature in black ink, appearing to read "Alexandra Scranton".

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



## Memorandum

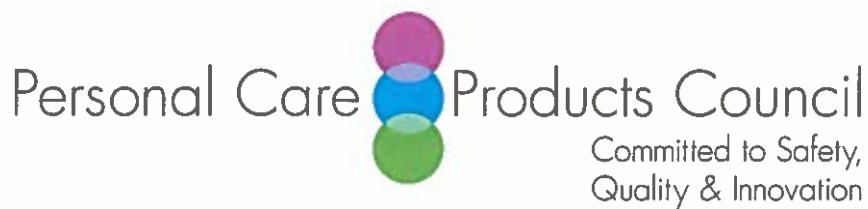
To: CIR Expert Panel Members and Liaisons  
From: Monice M. Fiume *MMF*  
Senior Director  
Date: November 28, 2018  
Subject: Wave 3 data for Alkoxylated Fatty Amides

Additional data have been received that address some of the data requested in the Insufficient Data Announcement (IDA) for this report. As a reminder, at the September meeting, the Panel found the data insufficient to determine safety for this group of ingredients, and an IDA was issued with the following data requests:

- Method of manufacture
- Impurities data
- Dermal absorption data on PEG-4 Rapeseedamide and PPG-2 Hydroxyethyl Cocamide;
  - if absorbed, then 28-day dermal toxicity data, as well as data on other toxicity endpoints, may be needed

Method of manufacture and impurities data for PEG-50 Hydrogenated Palmamide were received prior to the original mail date, and that information is included in the report you received earlier this month. The following have been received since that time and are included in this Wave 3 submission:

1. Anonymous. (2018) Process description PPG-2 Hydroxyethyl Coco/Isostearamide [*alkfat122018w3\_data 1*]
2. Anonymous. (2018) PPG-2 Hydroxyethyl Cocamide purity and impurities [*alkfat122018w3\_data 1*]
3. Anonymous. (2018) Method of manufacture PPG-2 Cocamide [*alkfat122018w3\_data 2*]



## Memorandum

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

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

**DATE:** November 20, 2018

**SUBJECT:** PPG-2 Hydroxyethyl Coco/Isostearamide and PPG-2 Hydroxyethyl Cocamide  
Anonymous. 2018. Process description PPG-2 Hydroxyethyl Coco/Isostearamide.  
Anonymous. 2018. PPG-2 Hydroxyethyl Cocamide purity and impurities.

2018

## Process Description

### PPG-2 Hydroxyethyl Coco/Isostearamide

#### Subject: Process Description



2018

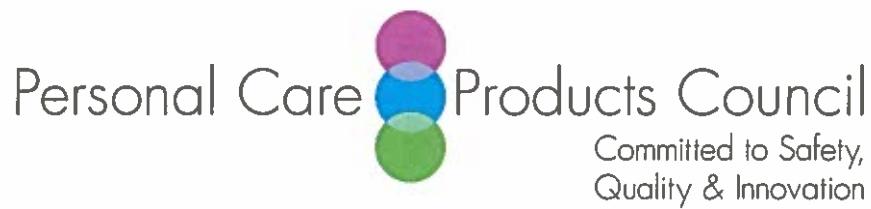
**PPG-2 Hydroxyethyl Cocamide >90% pure****Impurities:**

Methanol typically &lt;300 ppm

**Heavy metals**

testing for the listed heavy metals on several batches of the subject product found the following results:

Element	Results (ppm)
Lead (Pb)	<0.5
Arsenic (As)	<0.5
Mercury (Hg)	<0.5
Chromium (Cr)	<0.5
Antimony (Sb)	<0.5
Silver (Ag)	<0.5
Cobalt (Co)	<0.5
Copper (Cu)	<0.5
Nickel (Ni)	<0.5



**Memorandum**

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

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

**DATE:** November 26, 2018

**SUBJECT:** PPG-2 Cocamide

Anonymous. 2018. Method of manufacture PPG-2 Cocamide.

2018

### **Method of Manufacture PPG-2 Cocamide**

PPG-2 Cocamide is manufactured by propoxylated reaction of cocoyl monoisopropanol amide with approximately 1 mole propylene oxide. PPG-2 Cocamide is based on plant and synthetic raw materials.

**Impurity:**

Not detected.



Cosmetic  
Ingredient  
Review

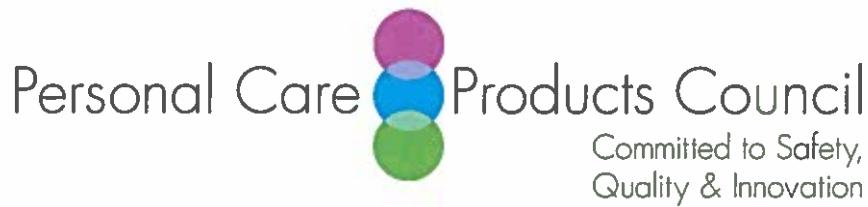
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Memorandum

To: CIR Expert Panel Members and Liaisons  
From: Priya Cherian, Scientific Writer/Analyst  
Date: November 28, 2018  
Subject: Wave 3 – Brown Algae

On November 28, 2018, new data regarding a trade name mixture containing Laminaria Digitata Extract (8-12%), that may address part of the insufficiencies of the Insufficient Data Announcement, were received. These data include composition, a Hen's Egg Test, a repeated insult patch test, and safety study summaries of acute oral, primary ocular irritation, primary skin irritation, and sensitization data. According to these data, the test substance was considered to be non-toxic ( $LD_{50} > 5$  g/kg in rats), non-sensitizing, and non-irritating to the eyes and skin. The relevant data has been attached herein and is labeled as *broalg122018data\_wave3*.



## Memorandum

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

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

**DATE:** November 28, 2018

**SUBJECT:** Laminaria Digitata Extract

Anonymous. 2018. Composition two trade name mixtures containing Laminaria Digitata Extract.

Consumer Product Testing Co. 2006. The Hen's Egg Test - Utilizing the Chorioallantoic Membrane (HET-CAM) (product 1 tested contains 8-12% Laminaria Digitata Extract).

Anonymous. Repeated insult patch test (product 1 tested contains 8-12% Laminaria Digitata Extract).

Anonymous. 1997. Safety study summary: Acute oral, primary ocular irritation, primary skin irritation and repeat insult patch test (product 2 tested ≤ 10% Laminaria Digitata Extract).

2010

**Product 1:**

In response to your request, we can confirm the composition is listed as follows:

<u>INCI Name</u>	<u>CAS#</u>	<u>EINECS#</u>	<u>Percent Range</u>	<u>Origin</u>
Urea	57-13-6	200-315-5	12% - 18%	
Synthetic Glucosamine HCl	66-84-2	200-638-1	10% - 15%	Veg.
Laminaria Digitata Extract <i>(aqueous extract)</i>	92128-82-0	289-980-0	8% - 12%	Veg.
Saccharomyces Cerevisiae Ext.	90046-12-1			
Water	84604-16-0	283-294-5	8% - 12%	Veg.
	7732-18-5	231-791-2	q.s. 100%	*****

Preservatives: Phenoxyethanol 0.8%

**Product 2:**

In response to your request, we can confirm the composition is listed as follows:

<u>INCI Name</u>	<u>CAS#</u>	<u>EINECS#</u>	<u>Percent Range</u>	<u>Origin</u>
Laminaria Digitata Extract <i>(aqueous extract)</i>	90046-12-1	289-980-0	≤ 10%	Veg.
Artemisia Vulgaris Extract	92128-82-0			
Water	84775-45-1	283-874-8	≤ 10%	Veg.
	7732-18-5	231-791-2	q.s. 100%	

Preservative: Phenoxyethanol 0.8%



Consumer Product Testing Co.

EST. 1975

## FINAL REPORT

**CLIENT:**

**ATTENTION:**

**TEST:**

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

Product I tested

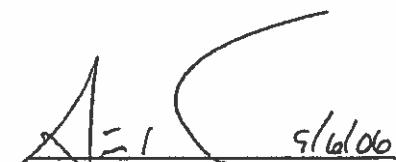
**TEST ARTICLE:**

( 8-12% Laminaria Digitata  
Extract )

**EXPERIMENT**

**REFERENCE NO.:**

V06-0176

  
5/6/06  
Steven Nitka  
Vice President  
Laboratory Director

This report is submitted for the exclusive use of the person, partnership, or corporation to whom it is addressed, and neither the report nor the name of these Laboratories nor any member of its staff, may be used in connection with the advertising or sale of any product or process without written authorization.

70 New Dutch Lane • Fairfield, New Jersey 07006-2514 • (973) 808-7111 • Fax (973) 808-7234



Consumer Product Testing Co.

EST. 1975

QUALITY ASSURANCE UNIT STATEMENT

Study No.: V06-0176

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of nonclinical laboratory studies. This study has been performed 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. The findings of this inspection may have been reported to management and the Study Director.

Quality Assurance:

Christine Hendricks 9/6/06  
Signature/Date

V06-0176  
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:**

**Reference Articles:**      Pure Petroleum Jelly

Body Lotion

<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.

**Method:**

Fresh, fertile, White Leghorn eggs were obtained from Moyer's Chicks, Inc., in Quakertown, Pennsylvania. They were stored at this facility for up to seven (7) days, at approximately 13° C ( $\pm 3^{\circ}$  C), before being incubated. For incubation the eggs were placed, on their sides, 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) for the ten (10) days of incubation. 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
Coagulation and/or Thrombosis		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.

V06-0176  
Page 5 of 6**Results:**

Test Article (%)	CAM #	Scores @				Total
		0.5 min.	2 min.	5 min.		
(5%)	1	0	0	0	0	0
	2	0	3	0	0	3
	3	5	0	0	0	5
	4	0	3	0	0	3
	Average:				2.75	

Reference Article (%)	CAM #	Scores @				Total
		0.5 min.	2 min.	5 min.		
Pure	1	0	0	0	0	0
Petroleum Jelly (50%)	2	0	0	1	0	1
	3	0	0	1	0	1
	4	0	0	1	0	1
	Average:				0.75	

Reference Article (%)	CAM #	Scores @				Total
		0.5 min.	2 min.	5 min.		
	1	0	0	0	0	0
	2	0	0	0	0	0
Body Lotion (50%)	3	0	0	1	0	1
	4	0	0	1	0	1
	Average:				0.50	

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

V06-0176  
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 reference articles were used to simulate a 100% reference article dosage in a rabbit eye. The Sponsor requested that his product be dosed at 5%. This test would be the equivalent of the article tested at 10% in the rabbit eye.

**Historical *In Vivo* Results:**

The reference products have historically been categorized as being practically non-irritating, eliciting scores approaching 0, at 24 hours, when dosed at 100% and tested using the Draize ocular irritation methodologies (Draize Scale: 0 - 110).

**Conclusion:**

Under the conditions of this test, the results indicate that the sponsor-submitted product,  
<sup>1</sup> at 10%, would have practically no ocular irritation potential *in vivo*.

**Professional personnel involved:**

Steven Nitka, B.S.	- Vice President
	Laboratory Director
	(Study Director)
Lillian Vazquez, B.S.	- Laboratory Supervisor
Melissa Fiuza, B.S.	- Technician
Christine Hendricks	- Senior Quality Assurance Associate

product I tested  
SAFETY REPORT (8-12 % Laminaria Digitata  
Extract)

## REPEATED INSULT PATCH TEST (RIPT)

### OBJECTIVE:

Consistent reapplication of consumer products or raw materials to areas of the skin may, under proper conditions, prove to be contact sensitizers or irritants in certain individuals. It is the intention of a Repeat Insult Patch Test (RIPT) to provide a basis for evaluation of this irritation/sensitization potential if such exists.

### SUMMARY:

One hundred (100) male or female panelists participate and complete this 21 days RIPT study. Nine inductive patchings are done over the study period and allergic reactions if any are observed by trained technicians.

### MATERIALS:

Description: The test material was supplied by the Sponsor  
to ensure protocol compliance. The testing was done on a 10%  
concentration of the raw material in an inert Carbopol vehicle.

#### Test Material Evaluation Prerequisite:

Prior to induction of a human test panel, animal toxicology, microbiology and other in-vivo or in-vitro performance spectra were required to assess the feasibility of commencement of the study.

Labeling: Test materials were properly labeled and identified as :

Application: Product was applied neat to the skin as indicated in the Procedure.

**PANEL SELECTION:**

**A. Recruitment:**

Subjects were recruited by advertisement in local papers, community bulletin boards, phone solicitation and placed in the testing facility subject data bank.

**B. Inclusion:**

Subjects were selected as per \_\_\_\_\_ Standard  
Operating Procedures. A minimum of (100) subjects completed the study.

1. Number/Sex 100 / Female or male subjects
2. Age 18-60 years of age

**C. Exclusion**

1. Subjects currently using or having used within the last six months Retin-A, or analogs, Corticosteroids, Benzoyl Peroxide, and Topical Anti-biotics.
2. Subjects having had facial peels or Dermabrasion within the last year.
3. Subjects with psoriasis, eczema, or atopic dermatitis.
4. Subjects currently on test in any other clinical study for topical or systemic medications or products.
5. Subjects with known communicable disease.
6. Subjects on medication will be reviewed on a case-by-case basis.
7. Subjects who are pregnant or intend to become pregnant within the next 60 days.
8. Subjects who are nursing / lactating.
9. Subjects who, in the opinion of the Principal Investigator, may express a negative reaction to a test sample based on medical or other pre-test conditions.

**D. Informed Consent form:**

An informed consent form was given to each subject prior to initiating a study. Each signed and dated form was filed at the testing laboratory.

**PROCEDURE:**

- Subjects are requested to bathe or wash as usual before arrival at the test center.
- 0.2 ml or 0.2 g of the test material was dispensed onto the occlusive, hypoallergenic patch\*.
- The patch was then applied directly to the skin of the infrascapular regions of the back, to the right or left of the midline and the subject was dismissed with instructions not to wet or exposed the test area to direct sunlight.
- After 24 hours, the patch was removed by the panelist at home.
- This procedure was repeated until a series of nine consecutive 24 hour exposures have been made for every Monday, Wednesday and Friday for three consecutive weeks.
- In the event of an adverse reaction, the area of erythema and edema will be measured. The edema was estimated by the evaluation of the skin with respect to the contour of the unaffected

normal skin. Reactions were scored just before applications two (2) through nine (9). In most instances this is approximately 24 hours after patch removal. Clients were notified immediately in the case of adverse reaction and determination was made to treatment program if necessary.

- Subjects were then given a 10-14 day rest period after which a challenge or retest dose was applied once to a previously unexposed test site. The retest dose was equivalent to any one of the original nine exposures.
- Reactions were scored 24 and 48 hours after application.
- Comparison was made between the nine sensitizing doses and the retest dose.

\* Patch description: Johnson & Johnson Bandages (30 x 30 mm Webril affixed to the center of a 40 x 40 mm adhesive bandage) or the equivalent.

#### SCORING SCALE FOR RIPT

0	- No evidence of any effect
0.5	- (Barely perceptible) minimal faint (light pink) uniform or spotty erythema
1	- (Mild) pink uniform erythema covering most of contact site
2	- (Moderate) pink/red erythema visibly uniform in entire contact area
3	- (Marked) bright red erythema with accompanying edema, petechiae or papules
4	- (Severe) deep red erythema with vesiculation or weeping with or without edema

#### RESULTS AND DISCUSSION:

##### Induction Phase

A cumulative response index (CRI) is calculated individually and averaged together for all 100 subjects. A maximal index would be 4.0 if all subjects reacted with a 4 on each day of the induction test period. Results are presented in Table 1.

As the results indicate, the averaged CRI for the test material is 0.030 indicating that it induced insignificant irritation.

##### Challenge Phase

No reactions whatsoever were observed during the challenge phase indicating that the test materials provided little potential for sensitization potential.

#### CONCLUSION:

Under the controlled conditions of this study, the test product at 10% concentration showed little if any potential for irritation or sensitization as tested by the accepted protocols, and therefore should be safe for use.

**ATTACHMENT**

**PROTOCOL**

## PROTOCOL

### REPEATED INSULT PATCH TEST (RIPT)

#### OBJECTIVE:

Consistent reapplication of consumer products or raw material to areas of the skin may, under proper conditions, prove to be contact sensitizers or irritants in certain individuals. It is the intention of a Repeat Insult Patch Test (RIPT) to provide a basis for evaluation of this irritation/sensitization potential if such exists.

#### SUMMARY:

One hundred (100) male or female panelists participate and complete this 21 days RIPT study. Nine inductive patchings are done over the study period and allergic reactions if any are observed by trained technicians.

#### MATERIALS:

Description: All test materials will be supplied by the Sponsor to ensure protocol compliance.

Test Material Evaluation Prerequisite: Prior to induction of a human test panel, animal toxicology, microbiology and other in-vivo or in-vitro performance spectra may be required to assess the feasibility of commencement of the study.

**PANEL SELECTION:**

**A. Recruitment:**

Subjects are recruited by advertisement in local papers, community bulletin boards, phone solicitation and placed in the testing facility subject data bank.

**B. Inclusion:**

Subjects will be selected as per Standard Operating Procedures. A minimum of (100) subjects will complete the study.

1. Number/Sex      100 / Female or male subjects
2. Age                18-60 years of age

**C. Exclusion**

1. Subjects currently using or having used within the last six months Retin-A, or analogs, Corticosteroids, Benzoyl Peroxide, and Topical Anti-biotics.
2. Subjects having had facial peels or Dermabrasion within the last year.
3. Subjects with psoriasis, eczema, or atopic dermatitis.
4. Subjects currently on test in any other clinical study for topical or systemic medications or products.
5. Subjects with known communicable disease.
6. Subjects on medication will be reviewed on a case-by-case basis.
7. Subjects who are pregnant or intend to become pregnant within the next 60 days.
8. Subjects who are nursing / lactating.
9. Subjects who, in the opinion of the Principal Investigator, may express a negative reaction to a test sample based on medical or other pre-test conditions.

**D. Informed Consent form:**

An informed consent form is given to each subject prior to initiating a study. Each signed and dated form is filed at testing laboratory.

**PROCEDURE:**

Patch description: Johnson & Johnson Bandages (30 x 30 mm Webril affixed to the center of a 40 x 40 mm adhesive bandage) or the equivalent.

- Subjects are requested to bathe or wash as usual before arrival at the test center.
- 0.2 ml or 0.2 g of the test material is dispensed onto the occlusive, hypoallergenic patch.

- The patch is then applied directly to the skin of the infrascapular regions of the back, to the right or left of the midline and the subject is dismissed with instructions not to wet or exposed the test area to direct sunlight.
- After 24 hours, the patch is removed by the panelist at home.
- This procedure is repeated until a series of nine consecutive 24 hour exposures have been made for every Monday, Wednesday and Friday for three consecutive weeks.
- In the event of an adverse reaction, the area of erythema and edema is measured. The edema is estimated by the evaluation of the skin with respect to the contour of the unaffected normal skin. Reactions are scored just before applications two (2) through nine (9). In most instances this is approximately 24 hours after patch removal. Clients are notified immediately in the case of adverse reaction and determination is made to treatment program if necessary.
- Subjects are then given a 10-14 day rest period after which a challenge or retest dose is applied once to a previously unexposed test site. The retest dose is equivalent to any one of the original nine exposures.
- Reactions are scored 24 and 48 hours after application.
- Comparison is made between the nine sensitizing doses and the retest dose.

#### SCORING SCALE FOR RIPT

- |     |   |
|-----|---|
| 0   | - No evidence of any effect   |
| 0.5 | - (Barely perceptible) minimal faint (light pink) uniform or spotty erythema    |
| 1   | - (Mild) pink uniform erythema covering most of contact site                    |
| 2   | - (Moderate) pink/red erythema visibly uniform in entire contact area           |
| 3   | - (Marked) bright red erythema with accompanying edema, petechiae or papules    |
| 4   | - (Severe) deep red erythema with vesiculation or weeping with or without edema |

#### **REPORT:**

A full report of all appropriate data, investigator interpretation and observation, individual data point and conclusion will be delivered to the Client within 2 weeks of completion of the study subject to terms of payment. All such information will be considered the Confidential and Proprietary Property of the Client and will not be disclosed to any parties without the Clients written authorization.

TABLE 1  
REPEAT INSULT PATCH TEST RESULTS (100 SUBJECTS)

49	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0	0	0
59	0	0	0	0	0	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0	0	0	0	0	0
61	0	0	0	0	0	0	0	0	0	0	0	0	0	0
62	0	0	0	0	0	0	0	0	0	0	0	0	0	0
63	0	0	0	0	0	0	0	0	0	0	0	0	0	0
64	0	0	0	0	0	0	0	0	0	0	0	0	0	0
65	0	0	0	0	0	0	0	0	0	0	0	0	0	0
66	0	0	0	0	0	0	0	0	0	0	0	0	0	0
67	0	0	0	0	0	0	0	0	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0	0	0	0	0	0	0
69	0	0	0	0	0	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0	0	0	0	0	0
76	0	0	0	0	0	0	0	0	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0	0	0	0	0	0
79	0	0	0	0	0	0	0	0	0	0	0	0	0	0
80	0	0	0	0	0	0	0	0	0	0	0	0	0	0
81	0	0	0	0	0	0	0	0	0	0	0	0	0	0
82	0	0	0	0	0	0	0	0	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0	0	0	0	0	0
85	0	0	0	0	0	0	0	0	0	0	0	0	0	0
86	0	0	0	0	0	0	0	0	0	0	0	0	0	0
87	0	0	0	0	0	0	0	0	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0	0	0	0	0	0	0	0
91	0	0	0	0	0	0	0	0	0	0	0	0	0	0
92	0	0	0	0	0	0	0	0	0	0	0	0	0	0
93	0	0	0	0	0	0	0	0	0	0	0	0	0	0
94	0	0	0	0	0	0	0	0	0	0	0	0	0	0
95	0	0	0	0	0	0	0	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0	0	0	0	0	0	0	0
97	0	0	0	0	0	0	0	0	0	0	0	0	0	0
98	0	0	0	0	0	0	0	0	0	0	0	0	0	0
99	0	0	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Avg	0	0	0	0	0	0	0	0	0.015	0.015	0	0	0	0

Total Score: 0.030

## SAFETY STUDIES SUMMARY

Product 2 tested ( $\leq 10\%$  Laminaria  
Digitated Extract)

1..... ACUTE ORAL TOXICITY

2..... PRIMARY OCULAR IRRITATION

3..... PRIMARY SKIN IRRITATION

4..... REPEAT INSULT PATCH TEST

**REPORT #: 1**

# **SAFETY STUDY REPORT**

## **ACUTE ORAL TOXICITY STUDY** **ON** **(20% Dilution)**

**STUDY #:** 97-018

**DATE:** Jan., 12, 1997

**REFERENCE:** Acute Oral Toxicity. FHS LA, 16 CFR 1500.3.

### **MATERIALS:**

**Description:** The test material was supplied by , to ensure protocol compliance.

#### **Test Material Evaluation Prerequisite:**

Prior to induction of a human test panel, animal toxicology, microbiology and other in-vivo or in-vitro performance spectra were required to assess the feasibility of commencement of the study.

**Labeling:** The test material was properly labeled as 20% and identified with lot number of 1108.

**ANIMALS:** Healthy, young adult Wistar derived albino rats weighing between 150 to 300 grams were obtained from ACE Animals, Inc., Boyertown, Pennsylvania. Five male and five female rats were selected for the dose level chosen for this study.

**DIET:** Purina Rat Chow. Feed and water were supplied ad-libitum. Animals are fasted 18-24 hours prior to dosing; feed and water are returned ad-libitum immediately thereafter. Records were kept of the food supplier, delivery date, feed identity, batch number (if available) and expiration date. No feed was used beyond its expiration date.

ENVIRONMENTAL CONDITIONS:

Prior to the test period the animals were each uniquely identified with sequentially numbered ear tags and individually housed in wire bottomed cages in a temperature controlled room with a 12 hour light / dark cycle. Feed and water were provided ad-libitum after dosing. Litter is changed not less frequently than every third day and more if deemed necessary. Floors are broom cleaned and mopped with disinfectant (Spartan Sterigent Germicidal Cleanser or Pine Multi-Purpose Disinfectant) on each day of litter removal. Newly received animals are quarantined in a separate area for a period of 24 hours or more if necessary to determine the health status, prior to assignment in the housing facility. The animals are then further conditioned for a period of not less than 4 additional days before testing commencement.

PROCEDURE:

Eighteen to twenty-four hours prior to dosing the rats were fasted. During the fast period water was allowed ad-libitum. After fasting rats were individually weighed. All body weights were recorded and individual doses calculated based on these weights. The test material was then delivered by gavage at a dose level of 5.0 g/kg body weight. The animals were individually and singly dosed by gavage using a 12-18 gauge stainless steel needle attached to an appropriately calibrated syringe. Once the material had been ingested completely, feed and water were provided ad-libitum. The rats were individually caged and observed for mortality or other signs of gross toxicity for 14 days. At the end of the test period, all surviving animals were weighed.

RESULTS:

As shown in Table 1, no significant changes are reported for each of the 10 rats tested.

**CONCLUSION:**

Under the controlled conditions of this study, the test product (20% Dilution) Lot #1108 when tested as indicated herein may be regarded as ORALLY NON-TOXIC according to the reference. LD<sub>50</sub> > 5 g/kg.

TABLE 1ACUTE ORAL TOXICITY

(20% Dilution)

Dosage: 5 g/kg

Animal #	Sex	Body Weight		Dosage	Dose Delivered*	Mortality	
		Initial	Final			Day	Autopsy
		(grams)	(grams)	(grams)	(ml)		
7243	M	245	247	1.22	1.46	NA	NA
7244	M	235	238	1.18	1.42	NA	NA
7245	M	257	254	1.29	1.55	NA	NA
7246	M	243	249	1.22	1.46	NA	NA
7247	M	221	218	1.11	1.33	NA	NA
Mean		240.2	241.2	1.20	1.45		
7654	F	226	213	1.13	1.36	NA	NA
7655	F	199	196	1.00	1.19	NA	NA
7656	F	232	246	1.16	1.39	NA	NA
7657	F	246	239	1.23	1.48	NA	NA
7658	F	216	211	1.08	1.30	NA	NA
Mean		223.8	221	1.12	1.34		

\* - 1 ml weights 1.02 gm.

NA - Not applicable.

**REPORT #: 2**

# SAFETY STUDY REPORT

## PRIMARY OCULAR IRRITATION STUDY ON (20% Dilution)

STUDY #: 97-023

DATE: Mar. 03,1997

REFERENCE: Primary Eye Irritation. FHS LA, 16 CFR 1500.42.

### MATERIALS:

Description: The test material was supplied by to ensure protocol compliance.

#### Test Material Evaluation Prerequisite:

Prior to induction of a human test panel, animal toxicology, microbiology and other in-vivo or in-vitro performance spectra were required to assess the feasibility of commencement of the study.

Labeling: The test material was properly labeled as "20% and identified with lot number of 1108.

ANIMALS: Six healthy, Adult New Zealand Whit Albino Rabbits (2.0 - 3.0 kg) from Sgarlats Rabbitry, Harvey's Lake, Pennsylvania.

DIET: Purina Rabbit Pellets. Feed and water were supplied ad-libitum prior to dosing and immediately thereafter. Records were kept of the food supplier, delivery date, feed identity, batch number (if available) and expiration date. No feed was used beyond its expiration date.

ENVIRONMENTAL CONDITIONS:

Prior to the test period the animals were each uniquely identified with metal ear tags and individually housed in wire bottomed cages in an environmentally controlled room with a 12 hour light / dark cycle. Feed and water were provided ad-libitum after dosing. Litter is changed not less frequently than every third day and more if deemed necessary. Floors are broom cleaned and mopped with disinfectant (Spartan Sterigent Germicidal Cleanser or Pine Multi-Purpose Disinfectant) on each day of litter removal. Newly received animals are quarantined in a separate area for a period of 24 hours or more if necessary to determine the health status, prior to assignment in the housing facility. The animals are then further conditioned for a period of not less than 4 additional days before test commencement.

PROCEDURE:

Six healthy, adult, albino rabbits exhibiting no ocular defects or corneal injury were selected for test. One-tenth of a milliliter (0.1 ml) of the test material was placed on the everted lower lid of one eye of each rabbit. The upper and lower lids were gently held together for one second before releasing, to prevent loss of the test material. The contralateral eye of each rabbit remained untreated and served as a control. Ocular lesions were evaluated by the method of Draize<sup>(1)</sup>.

The Draize scores were then classified according to Kay and Calandra<sup>(2)</sup>. Lesions were evaluated at 24 hours and 72 hours post instillation. A 2% fluorescein sodium solution, followed by wash with physiological saline solution, was utilized as necessary for ocular observations.

RESULTS:

As shown in Table 1, no significant changes are reported for each of the 6 rabbits tested.

**CONCLUSION:**

Under the controlled conditions of this study, the test product (20%  
DILUTION) Lot # 1108 when tested as indicated herein is considered to be a NON-IRRITATING to the eyes according to the reference.

**REFERENCE:**

- (1) Draize et al. J. Pharmacol. Exp. Ther. 83 : 377-390, 1944.
- (2) Kay & Calandra, J. Soc. Cos. Chem. 13 : 281-289, 1962.

SCALE FOR SCORING OCULAR LESIONS

## 1. Corneas:

(A) Opacity - degree if density (area most dense taken for reading)

No opacity.....	0
Scattered or diffused area, details of iris clearly visible.....	1
Easily discernible translucent areas, details of iris slightly obscured.....	2
Opalescent areas, no details of iris visible, size of pupil barely discernible	3
Opaque, iris invisible.....	4

(B) Area of cornea involved

One quarter of less, but not zero.....	1
Greater than one quarter, but less than half.....	2
Greater than half, but less than three quarters.....	3
Greater than three quarters, up to whole area.....	4

Score AxBx5

Total Maximum = 80

## 2. Iris:

(A) Values

Normal.....	0
Folds above normal, congestion, swelling, circumcorneal injection (any or all of these, or combination of any thereof) iris still reacting to light (sluggish reaction is positive).....	1
No reaction to light, hemorrhage, gross destruction (any or all of these).....	2

## 3. Conjunctivae:

(A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)

Vessels normal.....	0
Vessels definitely injected above normal.....	1
More diffuse, deeper crimson red, individual vessels not easily discernible...	2
Diffuse, beefy red.....	3

(B) Chemosis

No swelling.....	0
Any swelling above normal (included nictating membrane).....	1
Obvious swelling with partial eversion of lids.....	2
Swelling with lids about half closed.....	3
Swelling with lids about half to completely closed.....	4

(C) Discharge

No discharge.....	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals).....	1
Discharge with moistening of the lids and hairs just adjacent to lids.....	2
Discharge with moistening of the lids and hairs and considerable area around the eye.....	3

Score (A+B+C) x 2

Total Maximum = 20

**TOTAL MAXIMUM SCORE :** 110 represents the sum of all scores obtained for the cornea, iris and conjunctivae.

**TABLE 1**  
**PRIMARY EYE IRRITATION**

(20% Dilution)

Amount Test Material Used: 0.1 ml

Rabbit No:	6110			6111			6112			6113			6114			6115		
Sex:	M			M			M			F			F			F		
Induction Weight (Kg):	2.43			2.55			2.65			2.53			2.73			2.78		
Hours	24	48	72	24	48	72	24	48	72	24	48	72	24	48	72	24	48	72
I. Cornea																		
(A) Opacity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(B) Area	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AxBx5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
II. Iris																		
(A) Values	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AX5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
III. Conjunctivae																		
(A) Hyperemia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(B) Chemosis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(C) Discharge	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(A+B+C)x2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total I+II+III	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Mean: 0.00

MMTS: Maximum Mean Total Score = 0

MMTS Classification

0.0 - 0.5	Non-irritating
0.6 - 2.5	Practically non-irritating
2.6 - 15.0	Minimally irritating
15.0 - 25.0	Mildly irritating
25.1 - 50.0	Moderately irritating
50.1 - 80.0	Severely irritating
80.1 - 100.0	Extremely irritating
100.1 - 110.0	maximally irritating

**REPORT #: 3**

## ***SAFETY STUDY REPORT***

**PRIMARY SKIN IRRITATION STUDY**  
**ON** (20% Dilution)

**STUDY #:** 97-028

DATE: Mar. 16,1997

**REFERENCE:** Primary Skin Irritation. FHSRA, 16 CFR 1500.41

## MATERIALS:

Description: The test material was supplied to ensure protocol compliance.

### **Test Material Evaluation Prerequisite:**

Prior to induction of a human test panel, animal toxicology, microbiology and other in-vivo or in-vitro performance spectra were required to assess the feasibility of commencement of the study.

Labeling: The test material was properly labeled as "20% and identified with lot number of 1108.

**ANIMALS:** . Six healthy, Adult New Zealand Whit Albino Rabbits (2.0 - 3.0 kg) from Sgarlats Rabbitry, Harvey's Lake, Pennsylvania.

DIET: Purina Rabbit Pellets. Feed and water were supplied ad-libitum prior to dosing and immediately thereafter. Records were kept of the food supplier, delivery date, feed identity, batch number (if available) and expiration date. No feed was used beyond its expiration date.

ENVIRONMENTAL CONDITIONS:

Prior to the test period the animals were each uniquely identified with sequentially numbered metal ear tags and individually housed in stainless steel wire bottomed cages in an environmentally controlled room with a 12 hour light / dark cycle. Feed and water were provided ad-libitum after dosing. Litter is changed no less frequently than every third day and more if necessary. Floors are broom cleaned and mopped with disinfectant (Pine Multi-purpose disinfectant) on each day of litter removal. Newly received animals are quarantined for a period of 24 hours or more if necessary to determine the health status, prior to assignment in the housing facility. The animals are then further conditioned for a period of not less than 4 additional days before test commencement.

PROCEDURE:

Preparation of Animals:

Six healthy and well adapted adult New Zealand White Albino rabbits weighing between 2.0 and 3.0 kg each were used. Approximately 24 hours before testing the rabbits were prepared by clipping the trunk free of hair. After shaving and just before testing, the skin of each animal was evaluated for any anomalies by grading according to the scale of "FHLA, 16 CFR 1500.41". If any site scores greater than zero, that rabbit was rejected and replaced. Any newly grown fur is removed on the day of the test with care to avoid irritation to the skin.

Preparation of the Test Site and Application of the Test Substance:

Five-tenths of a milliliter (0.5 ml) of the test material was applied to a small area (approximately 6 cm<sup>2</sup>) of the previously cleared intact and abraded skin and covered with a occlusive gauze patch, which was held in place with non-irritating, non-sensitizing tape. The entire trunk of the animal was wrapped with a rubberized elastic bandage to retard evaporation and as an aid in maintaining the test patch in position.

Exposure Period:

Animals were exposed to the test substance as indicated for a period of 24 hours after which, bandages were removed and all test sites were gently wiped with a cloth to remove any residual test material. Animals were examined for signs of erythema and edema and the responses were scored at 24 hours after application and then again at 72 hours. Scoring was conducted in accordance with the reference. Observations to fully evaluate the reversibility or irreversibility may be extended to a maximum of 14 days after application.

**RESULTS:**

As shown in Table 1, no significant changes are reported for each of the 6 rabbits tested.

**CONCLUSION:**

Under the controlled conditions of this study, the test product (20%  
DILUTION) Lot # 1108 when tested as indicated herein is considered to be a NON-PRIMARY  
IRRITANT to the skin according to the reference.

**TABLE 1**  
**ERYTHEMA AND ESCHAR SCORES**  
**(20% Dilution)**

Amount Test Material Used: 0.5 ml

Rabbit No:	8110	8111	8112	8113	8114	8115						
Sex:	M	M	M	F	F	F						
Induction Weight (Kg):	2.73	2.65	2.51	2.43	2.67	2.54						
Reaction												
(Hours)												
	24	72	24	72	24	72	24	72	24	72	24	72
<b>SKIN SITES:</b>												
1. INTACT ERYTHEMA	0	0	0	0	0	0	0	0	0	0	0	0
(LEFT) EDEMA	0	0	0	0	0	0	0	0	0	0	0	0
Mean	0	0	0	0	0	0	0	0	0	0	0	0
2. ABRASION ERYTHEMA	0	0	0	0	0	0	0	0	0	0	0	0
(RIGHT) EDEMA	0	0	0	0	0	0	0	0	0	0	0	0
Mean	0	0	0	0	0	0	0	0	0	0	0	0

Primary Irritation Index (PII) of 24 and 72 hour scores :

PII = 0.00

#### Primary Skin Irritation Score

- |           |                             |
|-----------|-----------------------------|
| 0.0 - 0.5 | - Non-primary irritant      |
| 0.6 - 2.0 | - Mild primary irritant     |
| 2.1 - 5.0 | - Moderate primary irritant |
| 5.1       | - Severe primary irritant   |

**REPORT #: 4**

# ***SAFETY STUDY REPORT***

**REPEAT INSULT PATCH TEST**  
**ON** (20% Dilution)

**STUDY #:** 97-031

**DATE:** *Mar. 26, 1997*

## **OBJECTIVE:**

Consistent reapplication of consumer products or raw materials to areas of the skin may, under proper conditions, prove to be contact sensitizers or irritants in certain individuals. It is the intention of a Repeat Insult Patch Test (RIPT) to provide a basis for evaluation of this irritation/sensitization potential if such exists.

## **SUMMARY:**

One hundred (100) male or female panelists participate and complete this 21 days RIPT study. Nine inductive patchings are done over the study period and allergic reactions if any are observed by trained technicians.

## **MATERIALS:**

**Description:** The test material was supplied by to ensure  
protocol compliance.

### **Test Material Evaluation Prerequisite:**

Prior to induction of a human test panel, animal toxicology, microbiology and other in-vivo or in-vitro performance spectra were required to assess the feasibility of commencement of the study.

**Labeling:** The test material was properly labeled as "20%"  
and identified with lot number of 1108.

**PANEL SELECTION:**

**A. Recruitment:**

Subjects were recruited by advertisements in local papers, community bulletin boards, phone solicitation and placed in the subject data bank.

**B. Inclusion:**

Subjects were selected as per the Standard Operating Procedures of the testing facility. A minimum of (100) subjects completed the study.

1. Number/Sex 100 / Female or male subjects
2. Age 18-60 years of age

**C. Exclusion**

1. Subjects currently using or having used within the last six months Retin-A, or analogs, Corticosteroids, Benzoyl Peroxide, and Topical Anti-biotics.
2. Subjects having had facial peels or Dermabrasion within the last year.
3. Subjects with psoriasis, eczema, or atopic dermatitis.
4. Subjects currently on test in any other clinical study for topical or systemic medications or products.
5. Subjects with known communicable disease.
6. Subjects on medication will be reviewed on a case-by-case basis.
7. Subjects who are pregnant or intend to become pregnant within the next 60 days.
8. Subjects who are nursing / lactating.
9. Subjects who, in the opinion of the Principal Investigator, may express a negative reaction to a test sample based on medical or other pre-test conditions.

**D. Informed Consent form:**

An informed consent form was given to each subject prior to initiating a study. Each signed and dated form was filed at the testing laboratory.

PROCEDURE:

- Subjects are requested to bathe or wash as usual before arrival at the test center.
- 0.2 ml or 0.2 g of the test material was dispensed onto the occlusive, hypoallergenic patch\*.
- The patch was then applied directly to the skin of the infrascapular regions of the back, to the right or left of the midline and the subject was dismissed with instructions not to wet or exposed the test area to direct sunlight.
- After 24 hours, the patch was removed by the panelist at home.
- This procedure was repeated until a series of nine consecutive 24 hour exposures have been made for every Monday, Wednesday and Friday for three consecutive weeks.
- In the event of an adverse reaction, the area of erythema and edema will be measured. The edema was estimated by the evaluation of the skin with respect to the contour of the unaffected normal skin. Reactions were scored just before applications two (2) through nine (9). In most instances this is approximately 24 hours after patch removal. Clients were notified immediately in the case of adverse reaction and determination was made to treatment program if necessary.
- Subjects were then given a 10-14 day rest period after which a challenge or retest dose was applied once to a previously unexposed test site. The retest dose was equivalent to any one of the original nine exposures.
- Reactions were scored 24 and 48 hours after application.
- Comparison was made between the nine sensitizing doses and the retest dose.

\* Patch description: Bandages (30 x 30 mm Webril affixed to the center of a 40 x 40 mm adhesive bandage ) or the equivalent.

SCORING SCALE FOR RIPT

- |     |   |
|-----|---|
| 0   | - No evidence of any effect   |
| 0.5 | - (Barely perceptible) minimal faint (light pink) uniform or spotty erythema    |
| 1   | - (Mild) pink uniform erythema covering most of contact site                    |
| 2   | - (Moderate) pink/red erythema visibly uniform in entire contact area           |
| 3   | - (Marked) bright red erythema with accompanying edema, petechiae or papules    |
| 4   | - (Severe) deep red erythema with vesiculation or weeping with or without edema |

**RESULTS AND DISCUSSION:**

**Induction Phase**

A cumulative response index (CRI) is calculated individually and averaged together for all 100 subjects. A maximal index would be 4.0 if all subjects reacted with a 4 on each day of the induction test period. Results are presented in Tables 1 and the averaged total CRI score for the test material 20% was found to be 0.002.

As the results indicate, the test material has an averaged total CRI score of 0.002, indicating that it induced insignificant irritation.

**Challenge Phase**

No reactions whatsoever were observed during the challenge phase indicating that the test materials provided little potential for sensitization potential.

**CONCLUSION:**

Under the controlled conditions of this study, the test product 20% concentration showed little if any potential for irritation or sensitization as tested by the accepted protocols, and therefore should be safe for cosmetic use.

## TEST MATERIAL:

REPEAT INSULT PATCH TEST RESULTS  
(20% Dilution)

TEST DATE : 3/26/97

Subject	INDUCTION PHASE									CHALLENGE		Total CRI Score
	day 3	day 5	day 7	day 10	day 12	day 14	day 17	day 19	day 21	24 hrs	48 hrs	
1	0	0	0	0	0	0	0	0	0	0	0	0.0
2	0	0	0	0	0	0	0	0	0	0	0	0.0
3	0	0	0	0	0	0	0	0	0	0	0	0.0
4	0	0	0	0	0	0	0	0	0	0	0	0.0
5	0	0	0	0	0	0	0	0	0	0	0	0.0
6	0	0	0	0	0	0	0	0	0	0	0	0.0
7	0	0	0	0	0	0	0	0	0	0	0	0.0
8	0	0	0	0	0	0	0	0	0	0	0	0.0
9	0	0	0	0	0	0	0	0	0	0	0	0.0
10	0	0	0	0	0	0	0	0	0	0	0	0.0
11	0	0	0	0	0	0	0	0	0	0	0	0.0
12	0	0	0	0	0	0	0	0	0	0	0	0.0
13	0	0	0	0	0	0	0	0	0	0	0	0.0
14	0	0	0	0	0	0	0	0	0	0	0	0.0
15	0	0	0	0	0	0	0	0	0	0	0	0.0
16	0	0	0	0	0	0	0	0	0	0	0	0.0
17	0	0	0	0	0	0	0	0	0	0	0	0.0
18	0	0	0	0	0	0	0	0	0	0	0	0.0
19	0	0	0	0	0	0	0	0	0	0	0	0.0
20	0	0	0	0	0	0	0	0	0	0	0	0.0
21	0	0	0	0	0	0	0	0	0	0	0	0.0
22	0	0	0	0	0	0	0	0	0	0	0	0.0
23	0	0	0	0	0	0	0	0	0	0	0	0.0
24	0	0	0	0	0	0	0	0	0	0	0	0.0
25	0	0	0	0	0	0	0	0	0	0	0	0.0
26	0	0	0	0	0	0	0	0	0	0	0	0.0
27	0	0	0	0	0	0	0	0	0	0	0	0.0
28	0	0	0	0	0	0	0	0	0	0	0	0.0
29	0	0	0	0	0	0	0	0	0	0	0	0.0
30	0	0	0	0	0	0	0	0	0	0	0	0.0
31	0	0	0	0	0	0	0	0	0	0	0	0.0
32	0	0	0	0	0	0	0	0	0	0	0	0.0
33	0	0	0	0	0	0	0	0	0	0	0	0.0
34	0	0	0	0	0	0	0	0	0	0	0	0.0
35	0	0	0	0	0	0	0	0	0	0	0	0.0
36	0	0	0	0	0	0	0	0	0	0	0	0.0
37	0	0	0	0	0	0	0	0	0	0	0	0.0
38	0	0	0	0	0	0	0	0	0	0	0	0.0
39	0	0	0	0	0	0	0	0	0	0	0	0.0
40	0	0	0	0	0	0	0	0	0	0	0	0.1
41	0	0	0	0	0	0	0	0	0	0	0	0.0
42	0	0	0	0	0	0	0	0	0	0	0	0.0
43	0	0	0	0	0	0	0	0	0	0	0	0.0
44	0	0	0	0	0	0	0	0	0	0	0	0.0
45	0	0	0	0	0	0	0	0	0	0	0	0.0
46	0	0	0	0	0	0	0	0	0	0	0	0.0
47	0	0	0	0	0	0	0	0	0	0	0	0.0
48	0	0	0	0	0	0	0	0	0	0	0	0.0
49	0	0	0	0	0	0	0	0	0	0	0	0.0
50	0	0	0	0	0	0	0	0	0	0	0	0.0
51	0	0	0	0	0	0	0	0	0	0	0	0.0
52	0	0	0	0	0	0	0	0	0	0	0	0.0
53	0	0	0	0	0	0	0	0	0	0	0	0.0
54	0	0	0	0	0	0	0	0	0	0	0	0.0
55	0	0	0	0	0	0	0	0	0	0	0	0.0
56	0	0	0	0	0	0	0	0	0	0	0	0.0
57	0	0	0	0	0	0	0	0	0	0	0	0.0
58	0	0	0	0	0	0	0	0	0	0	0	0.0
59	0	0	0	0	0	0	0	0	0	0	0	0.0
60	0	0	0	0	0	0	0	0	0	0	0	0.0
61	0	0	0	0	0	0	0	0	0	0	0	0.0
62	0	0	0	0	0	0	0	0	0	0	0	0.0
63	0	0	0	0	0	0	0	0	0	0	0	0.0
64	0	0	0	0	0	0	0	0	0	0	0	0.0
65	0	0	0	0	0	0	0	0	0	0	0	0.0
66	0	0	0	0	0	0	0	0	0	0	0	0.0
67	0	0	0	0	0	0	0	0	0	0	0	0.0
68	0	0	0	0	0	0	0	0	0	0	0	0.0
69	0	0	0	0	0	0	0	0	0	0	0	0.0
70	0	0	0	0	0	0	0	0	0	0	0	0.0
71	0	0	0	0	0	0	0	0	0	0	0	0.0
72	0	0	0	0	0	0	0	0	0	0	0	0.0
73	0	0	0	0	0	0	0	0	0	0	0	0.0
74	0	0	0	0	0	0	0	0	0	0	0	0.0
75	0	0	0	0	0	0	0	0	0	0	0	0.0
76	0	0	0	0	0	0	0	0	0	0	0	0.0
77	0	0	0	0	0	0	0	0	0	0	0	0.0
78	0	0	0	0	0	0	0	0	0	0	0	0.0
79	0	0	0	0	0	0	0	0	0	0	0	0.0
80	0	0	0	0	0	0	0	0	0	0	0	0.0
81	0	0	0	0	0	0	0	0	0	0	0	0.0
82	0	0	0	0	0	0	0	0	0	0	0	0.0
83	0	0	0	0	0	0	0	0	0	0	0	0.0
84	0	0	0	0	0	0	0	0	0	0	0	0.0
85	0	0	0	0	0	0	0	0	0	0	0	0.0
86	0	0	0	0	0	0	0	0	0	0	0	0.0
87	0	0	0	0	0	0	0	0	0	0	0	0.0
88	0	0	0	0	0	0	0	0	0	0	0	0.0
89	0	0	0	0	0	0	0	0	0	0	0	0.0
90	0	0	0	0	0	0	0	0	0	0	0	0.0
91	0	0	0	0	0	0	0	0	0	0	0	0.0
92	0	0	0	0	0	0	0	0	0	0	0	0.0
93	0	0	0	0	0	0	0	0	0	0	0	0.0
94	0	0	0	0	0	0	0	0	0	0	0	0.0
95	0	0	0	0	0	0	0	0	0	0	0	0.0
96	0	0	0	0	0	0	0	0	0	0	0	0.0
97	0	0	0	0	0	0	0	0	0	0	0	0.0
98	0	0	0	0	0	0	0	0	0	0	0	0.0
99	0	0	0	0	0	0	0	0	0	0	0	0.0
100	0	0	0	0	0	0	0	0	0	0	0	0.092

AVERAGED TOTAL CRI SCORE



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### Memorandum

To: CIR Expert Panel Members and Liaisons

From: Jinqiu Zhu, PhD, DABT, ERT, CIR Toxicologist

Date: November 28, 2018

Subject: Exposure Parameters for the Inhalation Risk Assessment on Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

We are writing to you to provide some additional summary of the relevant RIVM data/estimates, particularly with regard to distributions of values considered. At the September 2017 meeting, the Panel issued an insufficient conclusion with the following data also needed:

- Consumer use data on pump and propellant hair sprays, for use in determining the extent of exposure to Polyaminopropyl Biguanide during product use.

To date, CIR has not received such consumer use data. In the strategy memo submitted to the Panel on Nov 19, 2018, exposure parameters used for inhalation exposure calculation of pump hair spray were clarified.

Although the most recent Council survey of maximum reported use concentrations by product category (updated on July 18, 2017) indicates that Polyaminopropyl Biguanide is no longer being used in pump or propellant hair sprays,<sup>1</sup> 2017 FDA VCRP data indicate that Polyaminopropyl Biguanide is being used in the Other Fragrance Preparations product category (use concentration data unavailable).<sup>2</sup>

Given the potential for inhalation exposure, CIR performed a risk assessment using the ConsExpo Web Spray Model (Consumer Exposure Model, Web version 1.0).<sup>3</sup> The maximum concentrations of use (0.0004% in propellant hair sprays and 0.053% in pump hair sprays) included in the inhalation risk assessment to estimate the inhalation exposure concentrations of Polyaminopropyl Biguanide during the use of cosmetic spray products were based on results from a previous Council survey that were submitted (April 11, 2017) to the CIR.<sup>4</sup>

Conservative default values published by Rijksinstituut voor Volksgezondheid en Milieu (RIVM – the Dutch National Institute for Health and Environment) were used in the calculations of the inhalation risk assessment.<sup>5,6</sup> These exposure parameters are listed below for the Panel's review. One exception is that the room ventilation rate was assumed to be 0.2/hr, which is the default value specified in REACH guidance, rather than 2/hr indicated by RIVM guidance for bathrooms. The more conservative value (0.2/hr) appears to be more appropriate to represent low-end air-exchange rates in homes in the US, in which ventilation fans may not be used routinely.

No default values are available specifically for pump hair spray products. Thus, the spray duration assumed for propellant hair sprays (14.4 sec) and default values for pump toilet-water sprays were used in the calculations for pump hair sprays.

**Direction of spraying:** Towards exposed person

**Exposure duration/event:** 5 min

**Room volume:** 10 m<sup>3</sup>

**Room height:** 2.5 m

**Room ventilation rate:** 0.2/hr

**Cloud Volume:** 0.0625 m<sup>3</sup>

**Density non-volatile:** 1.5 g/cm<sup>3</sup>

**Inhalation cut-off diameter:** 15 µm

**Spray duration:** 14.4 sec for pump/propellant hair spray and 10.2 sec for deodorant spray

**Initial median aerosol droplet diameter** (Coefficient of Variation): 46.5 (2.1), 2.7 (0.73)\* and 8.3 (0.84) µm for propellant hair spray, pump hair spray and propellant deodorant spray, respectively.

**Mass generation rate:** 0.4, 0.1\* and 0.45 g/sec for propellant hair spray, pump hair spray and propellant deodorant spray, respectively.

**Airborne fraction:** 0.2, 0.02\* and 0.9 g/g for propellant hair spray, pump hair spray and propellant deodorant spray, respectively.

*\*No default values are available specifically for pump hair spray products. Spray parameter default values developed for pump toilet water sprays assumed adequate for calculating conservative estimates of exposures from pump hair sprays.*

The average Polyaminopropyl Biguanide inhalation exposure concentrations, estimated using the ConsExpo Web Spray model, were 0.00012, 0.0022 and 0.00024 mg/m<sup>3</sup> for propellant hair spray, pump hair spray and propellant deodorant spray, respectively. The margin of safety (MOS) calculation was based on a no observed adverse effect concentration (NOAEC) at 0.024 mg/m<sup>3</sup>, derived from a 28-day inhalation study in which rats were exposed, nose only, to Polyaminopropyl Biguanide in an aerosolized water solution, 6 h/day, 5 days/week. The MOS values were 200, 11 and 100 for propellant hair spray, pump hair spray and propellant deodorant spray, respectively.

According to the Comments regarding the aerosol particle size data, submitted by CIR Science and Support Committee (SCC) on Oct 30, 2018, to the December meeting, the particle/droplet size of pump sprays is generally larger than aerosols.<sup>8</sup> Therefore, the median aerosol droplet diameter data of propellant hair spray (46.5 µm) can be used for pump hair spray. Accordingly, the ConsExpo model yielded an average Polyaminopropyl Biguanide inhalation exposure concentration of 0.00038 mg/m<sup>3</sup> for pump hair spray, which results in a MOS of 63.

#### References:

1. Personal Care Products Council. Updated concentration of use by FDA product category: Polyaminopropyl Biguanide (PHMB). Unpublished data submitted by the Personal Care Products Council on 7-18-2017. 2017. pp.1-2.
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6. RIVM (Dutch National Institute for Health and Environment). New default values for the spray model. Bilthoven, 2017. Report No. RIVM, March 2010. pp. 1-4.
7. CIR Science and Support Committee of the Personal Care Products Council (CIR SSC). 10-30-2018. Comments on Draft Revised CIR Precedent - Aerosols Document/Submission of Aerosol Particle Size Data.
8. Rothe H, Fautz R, Gerber E, et al. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. Toxicol Lett. 8-28-2011;205(2):97-104. PM:21669261.



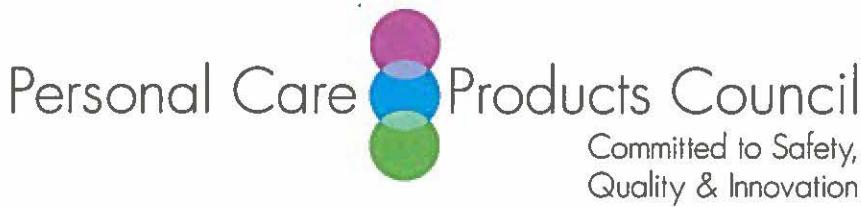
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**MEMORANDUM**

To: CIR Expert Panel Members and Liaisons  
From: Bart Heldreth, Ph.D., Executive Director, Cosmetic Ingredient Review  
Subject: 149<sup>th</sup> Meeting of the CIR Expert Panel — Monday and Tuesday, December 3-4, 2018  
Date: November 28, 2018

Additional comments have been received this week from the Council, which will be distributed at the meeting. However, for those final reports with substantive comments, we have included those herein, to ensure that they will be part of your assessments. Comments on the following reports are thus included:

- Acrylates Copolymers
- Vinylpyrrolidone Polymers
- Salicylic Acid and Salicylates



## Memorandum

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

**FROM:** Alexandra Kowcz, MS, MBA  
Industry Liaison to the CIR Expert Panel

**DATE:** November 26, 2018

**SUBJECT:** Draft Final Report: Amended Safety Assessment of Acrylates Copolymers as Used in Cosmetics (draft prepared for the December 3-4, 2018 CIR Expert Panel Meeting)

The Council respectfully submits the following comments on the draft final report, Amended Safety Assessment of Acrylates Copolymers as Used in Cosmetics.

### Key Issues

Regulations affecting cosmetic ingredients based on environmental concerns have been included in the Cosmetic Use section in previous reports, e.g., Hydrofluorocarbon 152a.

Therefore, to acknowledge that Polymethyl Methacrylate has had use in cosmetics as "microbeads", please add the following to the Cosmetic Use section. "Based on environmental concerns, the use of microbeads in cosmetics is being phased out in many jurisdictions including the United States. Microbeads includes the Polymethyl Methacrylate beads described in the 2011 CIR report." FDA's web page on microbead-free waters act

<https://www.fda.gov/cosmetics/guidanceregulation/lawsregulations/ucm531849.htm> provides additional details and appropriate references for this action in the United States. If the note is left in the Method of Manufacture section with the summary from the original CIR report on Polymethyl Methacrylate, what will happen to this note in the published report when the italicized text is deleted? If the note concerning microbeads is left in the method of manufacture section, a reference should be added.

The Introduction states that the safety of C10-30 Alkyl Acrylate Crosspolymer polymerized in benzene is not included in this report. It would be helpful if the Introduction also stated why the CIR Expert Panel considered the data insufficient to support the safety of C10-30 Alkyl Acrylate Crosspolymer polymerized in benzene. With a description of the risk assessment in the Introduction, the risk assessment section concerning C10-30 Alkyl Acrylate Crosspolymer polymerized in benzene could be deleted.

Additional Considerations

Composition/Irrurities, VA/Butyl Maleate/Isobornyl Acrylate Copolymer - Please delete "dimethylformaldehyde" as it is another name for acetone (as stated in the NICNAS assessment [reference 8] and the Dictionary).

Cosmetic Use - Please correct: "in products that can be used near the eye" to "in products that are used near the eye"

Short-Term, Acrylates Copolymers old report summary - Please include the concentration and the time of exposure (hours/day, days/week, duration).

Short-Term, Oral, Acrylates Copolymers - In the description of the 28-day study in minipigs, both "cecum" (generally used in the United States) and "caecum" are used. Please pick one spelling and use it consistently throughout the report.

Subchronic, Acrylates Copolymers original report summary - Please include details about the exposure (hours/day, days/week, duration) and exposure concentration.

Chronic, Acrylates Copolymers original report summary - Please include the species and details about the exposure (hours/day, days/week, duration) and exposure concentration.

DART, Acrylates Copolymers original report summary - Development is the focus of studies in which animals were dosed only during gestation. Therefore, for studies with dosing only during gestation, it should state developmental effects rather than reproductive effects were not observed. If rats were dosed on gestation days 6-15, how could they be "killed on day 10 of gestation"? Perhaps "day 10" should be "day 20".

Dermal Irritation and Sensitization, Acrylates Copolymer old report summary; Ocular Irritation, Acrylates Copolymer old report summary - As "alternative methods" include *in vitro*, *in silico*, read-across and other methods, please use a more specific term, e.g., *in vitro*, than "an alternative method".

Ocular Irritation, Acrylates Copolymer old report summary - Please correct: "not corrosive according to OECD guidelines, by [should be but] considered minimally irritating..."

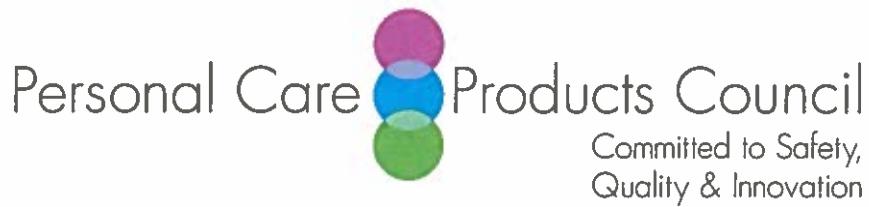
Summary - Please delete the following sentence as which report was reviewed concurrently will not be known by the time the report is published: "Additionally, the Panel determined that three acrylates copolymers that were included in the original report should be excluded here because these are already under review in a concurrent safety assessment." If this sentence is left in the Summary, the identity of the three polymers not included in the report should be stated.

Please include the route of exposure used in the micronucleus test.

Discussion - As new ingredients are always being added to the Dictionary, please delete: "and there are some that will warrant a review of their own in the near future because of frequency of use."

What is "the established threshold limit value for nasal irritation" for acrylic acid? It should be presented earlier in the report.

Conclusion - As this is a draft final report, the conclusion needs to be updated as it still says: "The Panel issued a tentative amended report for public comment..."



## Memorandum

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

**FROM:** Alexandra Kowcz, MS, MBA  
Industry Liaison to the CIR Expert Panel

**DATE:** November 26, 2018

**SUBJECT:** Draft Final Report: Amended Safety Assessment of Salicylic Acid and Salicylates as Used in Cosmetics (draft prepared for the December 3-4, 2018 CIR Expert Panel Meeting)

The Council respectfully submits the following comments on the draft final report, Amended Safety Assessment of Salicylic Acid and Salicylates as Used in Cosmetics.

### Key Issues

As Hexyl Salicylate is a fragrance ingredient with an IFRA standard it should be removed from the report. If Hexyl Salicylate is left in the report, the IFRA standard should be presented in the Cosmetic Use section and the values for all product categories should be stated.

The Council expects IFRA standards to be followed for all functions.

In the Cosmetic Use section, the EU regulations for salicylates and Salicylic Acid should be presented separately from the recent preliminary SCCS opinion on Salicylic Acid. The preliminary opinion has not been finalized and has not been incorporated into the EU cosmetic regulations as implied by the current presentation of this information in the CIR report. Salicylic Acid is not included in EU Annex II (list of substances which cosmetic products must not contain) as stated in the CIR report. Salicylic Acid is included in EU Annex III, the list of restricted ingredients. This needs to be corrected.

The exposure assessment that assumes use of a peel in a manner similar to a shower gel should be deleted from the report (including from the Summary). Actual exposure data (plasma concentrations of Salicylic Acid -  $C_{max}$  0.81  $\mu\text{g}/\text{mL}$ ) from use of a peel product containing 30% Salicylic Acid are available. The actual data should be used. In addition to comparing plasma Salicylic Acid from the use of a peel containing 30% Salicylic Acid to an oral dose of 650 mg aspirin ( $C_{max}$  56.4  $\mu\text{g}/\text{mL}$ ), the exposure from use of a peel could be compared to blood concentrations considered to be toxic (Case Reports section states that salicylism occurs at concentrations greater than 35 mg/dL and the Other Clinical Reports section states that blood concentrations  $>300 \mu\text{g}/\text{mL}$  should be considered toxic). The exposure studies (reference 54, 57, 59) need to be added to the Summary.

### Additional Considerations

Introduction - It is not clear why Butyloctyl Salicylate and Hexylidodecyl Salicylate are not in the list of esters as they are esters, e.g., chemical class listed in the *Dictionary* is esters.

Cosmetic Use - It should be made clear that sunscreens are considered cosmetics in Europe, but are OTC drugs in the United States.

Noncosmetic Use, Ethylhexyl Salicylate - This section should state that when Ethylhexyl Salicylate is used as a sunscreen in the United States, it must be labeled Octisalate.

Dermal Penetration, Ethylhexyl Salicylate and Salicylic Acid - What does "total absorption" represent (reference 14)?

Dermal Penetration, Ethylhexyl Salicylate - Was any Ethylhexyl Salicylate recovered in the receptor fluid (reference 27)?

Dermal Penetration, Methyl Salicylate - What does "skin penetration" represent (reference 30)? Is it the amount just in the receptor fluid, or does it also include what was recovered in the skin?

Dermal Penetration, Salicylic Acid - What is meant by "dermal absorption" (reference 4)?

Dermal Penetration, Animal and Human, old report summaries - How long after exposure does about 10% of applied salicylates remain in the skin?

Dermal Penetration, Human, Methyl Salicylate - It is not clear what is meant by "or to very high doses" (reference 36).

ADME, Placental - The human placental perfusion study is published and should be cited to the original reference rather than the preliminary SCCS opinion.

Acute, Dermal, old report summary - What is meant by "Little acute toxicity", e.g., deaths, clinical signs?

Short-Term, Oral, Methyl Salicylate - Did the NTP really complete two 14 day studies of Methyl Salicylate in CD-1 mice? The protocols are the same and the titles of the references (43, 44) are the same.

Short-Term Oral, Sodium Salicylate, old report summary - What happened to the dogs that were treated with 10% aqueous Sodium Salicylate for 2 weeks?

Subchronic, Oral, old report summaries - Please include some indication of dose in the old report summaries. Please revise: "No treatment related observations were observed."

DART, Animal, Oral, Sodium Salicylate, last paragraph - Were the significant differences in body and tail length and mean body weight increases or decreases?

Risk Assessment - Reference 53 is the SCCNFP opinion not the preliminary SCCS opinion. The 75 mg/kg/day NOAEL was used in both opinions.

Risk Assessment, Oral, Salicylic Acid, old report summary - As a new exposure assessment is being added to this report, the summary of the exposure assessment included in the original report should be deleted.

Estrogenic Activity - Please correct: "the nature hormone estradiol"

Sensitization, In Vitro - Please identify the types of *in vitro* sensitization assays that were used (reference 74).

Sensitization, Animal - What was the EC<sub>3</sub> for Hexyl Salicylate (it says "very low")?

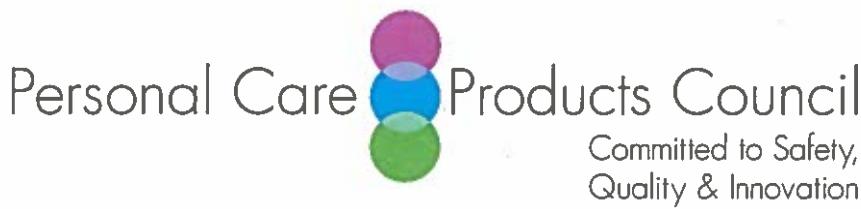
Sensitization, Human - A skin sensitization NOEL is usually called a NESIL (No Expected Sensitization Induction Level).

**Computational Analyses/Predictions** - This section concerns sensitization and should be presented after the Sensitization section rather than the Phototoxicity/Photosensitization section.

**Summary** - Please add the conclusion for MEA-Salicylate to the Summary.

When discussing dermal penetration what is meant by “relatively low”?

Please correct “Amyl Acetate” to “Amyl Salicylate”



## Memorandum

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

**FROM:** Alexandra Kowcz, MS, MBA  
Industry Liaison to the CIR Expert Panel

**DATE:** November 26, 2018

**SUBJECT:** Draft Final Report: Safety Assessment of Vinylpyrrolidone Polymers as Used in Cosmetics (draft prepared for the December 3-4, 2018 CIR Expert Panel Meeting)

The Council respectfully submits the following comments on the draft final report, Safety Assessment of Vinylpyrrolidone Polymers as Used in Cosmetics.

**Memo;** Cytotoxicity - The Council's previous statement that the PVP modified with a hydrophobic group, such as octadecyl or di(dodecyl), are not cosmetic ingredients is based on the lack of an INCI name for these materials in the *International Cosmetic Ingredient Dictionary* and by the paper in which the information on these materials was found (reference 40 of the CIR report). This reference states that the modified PVP polymers are used as a drug delivery systems for the treatment of cancer, inflammation, diabetes and allergy. This paper does not mention potential use in cosmetic products. Perhaps reference 40 should be cited to indicate how the authors of this paper said these materials were used. As these materials are not PVP, the studies on them should not be presented under a PVP subheading.

**Abstract;** Conclusion - As stated in comments previously provided by the Council, "intended use" should apply to the use of the cosmetic products, not the use of the ingredient.

**Composition/Impurities,** VP Acrylates Copolymers - The "/" is missing from VP/Dimethylaminoethylmethacrylate Copolymer in the heading and the sentence below the heading.

**Cosmetic Use;** Summary - The word "category" needs to be added to the end of the first paragraph. The use concentration of 50% VP/VA Copolymer in hair care products included in the original report should also be stated in the Cosmetic Use section and the Summary.

The presentation of 9 ingredients not in use is not consistent with the report on alkyl lactyl lactate salts. In that report, three ingredients are included in a table, in this report nine ingredients are included in the text as a list.

DART, PVP old report summary - What was the age of the rabbit embryos used in the *in vitro* study?

Ocular Irritation, PVP, old report summary - Is the re-review (reference 7) the correct reference?

Although this information may have been in studies considered for the re-review, none of it can actually be found in the re-review. The original references should be cited.

Discussion - The following sentence about the insufficient data ingredients does not make sense and needs to be revised. "The subgroup of 3 vinylpyrrolidone polymers for which data are insufficient to determine safety comprise, in part the residues of urethane monomers; and the data need for the subgroup are:..." (this sentence appears to be saying that the polymers comprise the monomers).