




**QUANTITATIVE RISK ASSESSMENT OF SKIN SENSITIZATION INDUCTION
FROM FRAGRANCE EXPSOURES**



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November 30, 2019

1. INTRODUCTION

Cardno ChemRisk was asked by WEN By Chaz Dean (“WCD”) to conduct a comprehensive risk and safety assessment of the cosmetic product commonly known as WEN® by Chaz Dean Cleansing Conditioner (the “WEN Products”), and, specifically, whether the product causes hair loss and/or any other adverse dermal event, which evaluation was triggered by complaints and allegations that the WEN Products caused hair loss in a very small percentage of consumers. As part of that comprehensive risk and safety assessment, we performed a QRA for skin sensitization induction potential based on daily exposure to fragrances from the use of common rinse-off and leave-on personal care and cosmetic products to determine the safety efficacy of the restricted use limits for fragrances.

This analysis was performed because fragrances are used in a wide variety of personal care and cosmetic products resulting in a high potential for exposure in the general population. Fragrance chemicals commonly used in personal care products have been shown to induce skin sensitization and allergic contact dermatitis at sufficient levels of exposures (de Groot et al. 1997; Cheng et al. 2014). As a result, product-specific restricted use limits for fragrances with skin sensitization potential have been developed to limit consumer exposure and reduce the potential for adverse health effects. These limits for individual fragrances are based upon a quantitative risk assessment (QRA) conducted by Api et al. (2008a; 2008b) and published by the International Fragrance Association (IFRA). However, recent data has suggested that the incidence of contact allergy associated with fragrances has not significantly decreased since the introduction of these limits (Kimber et al. 2017). Additionally, there have been some reports of potential skin irritation and allergic contact dermatitis associated with the use of some personal care and cosmetic products, including WEN by Chaz Dean, Inc. (WCD) cleansing conditioners (Kwa et al. 2017).

2. METHODS

2.1. Identification of fragrances for evaluation

Product formulation sheets for two versions of the WEN Products (Sweet Almond Mint and Pomegranate) as well as Material Safety Data Sheets for the listed ingredients in each product were reviewed to develop a list of fragrance chemicals present in the products. Those fragrances with restricted use limits based on sensitization potential were identified from the database maintained by the International Fragrance Association (IFRA) (www.ifraorg.org/en-us/standards). IFRA is a trade organization that with members that account for 90% of the global production of fragrances. One of the tenets of the organization is to rigorously assess the toxicity and allergenicity of fragrance ingredients. Once identified, those fragrances were evaluated further.

2.2. Calculation of consumer exposure level

A critical parameter to any risk assessment is exposure assessment. An estimated daily dermal exposure to fragrance chemicals, also known as a consumer exposure level (AEL) was calculated using the following equation and associated parameters:

$$CEL = \frac{(MDE)(A)(RF)(C\%)}{SA}$$

CEL: consumer exposure level ($\mu\text{g}/\text{cm}^2/\text{day}$)

MDE: product-specific maximum dermal exposure ($\mu\text{g}/\text{application}$)

A: product-specific mean number of applications per day (applications/day)

RF: product-specific retention factor, or percent of product remaining on the skin

C%: product-specific weight fraction (% weight/volume) of fragrance chemical

SA: surface area of body site where product in applied (cm^2)

Product-specific data on the amount of product applied per application and the mean number of application per day were collected from a series of consumer use studies of adult woman in the U.S. (Loretz et al. 2005; Loretz et al. 2006; Loretz et al. 2008). Adult female body part-specific surface areas were used in the calculation (EPA 2011; Cadby et al. 2002; Cowan-Ellsberry et al. 2008; Ferrario et al. 2000; SCCS 2016). Further, it was assumed that various personal care and cosmetic products examined in this study contained the maximum recommended concentration for each fragrance chemical by category as presented in the IFRA standards.

2.3. Risk characterization

In order to characterize risk, the CEL was compared to the acceptable exposure level (AEL), or an exposure that is not expected to induce skin sensitization in consumers. The AEL is calculated by applying uncertainty or safety assessment factors (SAF) to the no expected sensitization induction level (NESIL) for each fragrance. A margin of safety (MOS) was calculated using the following equation:

$$MOS = \frac{AEL}{CEL} = \frac{NESIL/SAF}{CEL}$$

A MOS of greater than 1.0 represents a low likelihood of sensitization induction from exposure to the selected fragrance in the evaluated product type. Whereas, a MOS greater than 1.0 suggests a potential risk for sensitization induction.

3. RESULTS

[REDACTED]

A total of 40 fragrance chemicals present in the WEN Products. Of these, 11 had restricted use limits issued by IFRA based upon sensitization potential. These 11 were further evaluated for potential exposure and risk characterization among various personal care and cosmetic products (Table 1). WoE NESIL values for these fragrance chemicals ranged from 24 $\mu\text{g}/\text{cm}^2/\text{day}$ (methyl-2-nonynoate) to 29,500 $\mu\text{g}/\text{cm}^2/\text{day}$ (citronellol).

The parameters used to calculate the mean and 95th percentile amounts of product per application in terms of skin surface area are presented in Table 2. In those instances where the applied product exceeded the amount of product capable of adhering to the skin, exposure was limited to 10 mg/cm^2 for subsequent CEL calculations for that product.

Mean and 95th percentile CEL values were calculated for each of the 11 fragrance chemicals under evaluation. The results for [REDACTED] are presented as an example in [REDACTED]. The product-specific values for retention factor, applications per day, and amount of product per application based on skin surface area remained constant across all fragrance chemicals evaluated. Therefore, the product-specific CEL for an individual fragrance was determined by the restricted limit concentration [weight volume (%)] of the fragrance in the evaluated product. In general, those fragrance chemicals, such as [REDACTED] which are considered more potent sensitizers (e.g. lower NESILs), were restricted to lower concentration limits of use and thus showed lower CELs compared to fragrances with higher NESILs (i.e. lower sensitization potential).

Product-specific MOS calculations for [REDACTED] (as an example) are presented in [REDACTED]. Similar results were observed for nearly all the ten other fragrances under evaluation. Product-specific MOS values for all evaluated fragrances are presented in Table 4. Only one fragrance chemical, [REDACTED] had MOS values greater than 1.0 for both mean and 95th percentile exposure scenarios for all products. MOS values less than 1.0 were consistently observed across nearly all fragrances, except the aforementioned [REDACTED] for several product exposure scenarios including: the 95th percentile exposure for lipstick, 95th percentile exposure for solid antiperspirant, 95th percentile exposure for eye shadow, mean and 95th percentile exposure for face cream, and 95th percentile exposure for liquid foundation. Although MOS values for other exposure scenarios with leave-on products were greater than 1.0, they were considerably less than those for rinse-off products.


4. DISCUSSION AND CONCLUSION

In this study, Cardno ChemRisk evaluated the potential for fragrance chemicals present in the WEN Products to induce skin sensitization among consumers. Specifically, a quantitative risk assessment approach was utilized to examine the sensitization induction potential of select fragrance chemicals present in various leave-on and rinse-off products. It was assumed that these products contained the maximum recommended concentration of the evaluated fragrance chemicals per standards issued by the fragrance industry. The results of this analysis show that while rinse-off products (facial cleanser, body wash, shampoo, and conditioner) are not likely to induce skin sensitization, exposures resulting from use of leave-on products (e.g. face cream, body lotion) may result in an increased risk of skin sensitization induction among high-use

consumers. More specifically, these results indicate that the use of the WEN Products, which are rinsed off the scalp, would not be associated with an increased risk of skin sensitization induction due to exposure to the fragrances in the products. In addition, these results suggest that the maximum use limits for fragrances in certain leave-on personal care products may need to be re-evaluated.

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Table 2. Product-specific exposure parameters used to determine consumer exposure level (CEL)

Product	Amount per application (g)		Skin Surface Application Area (cm ²)	Notes	Amount of product per application (mg/cm ²) ^[a]	
	Mean	95 th Percentile			Mean	95 th Percentile
Lipstick	0.01	0.037	4.8	Total vermillion area	2.1	7.7
Solid antiperspirant	0.61	1.67	129	Axilla x 2	4.7	<i>12.9</i>
Eye shadow	0.03	0.096	24	Eye shadow area	1.3	4.0
Body lotion	4.42	10.22	17,360	Total body area - head area	0.3	0.6
Hair spray (aerosol)	2.58	7.42	800	Scalp area	3.2	9.3
Hair spray (pump)	3.64	10.95	800	Scalp area	4.6	<i>13.7</i>
Face cream	1.22	2.97	340	Head area - scalp area	3.6	8.7
Liquid foundation	0.54	1.7	340	Head area - scalp area	1.6	5.0
Hair conditioner (leave-on)	13.13	32.43	800	Scalp area	<i>16.4</i>	<i>40.5</i>
Shampoo	11.76	27.95	800	Scalp area	<i>14.7</i>	<i>34.9</i>
Body wash	11.3	24.3	17,700	Total body area - scalp area	0.6	1.4
Facial cleanser	2.57	5.89	340	Head area - scalp area	7.6	<i>17.3</i>
Hair conditioner (rinse-off)	13.13	32.43	800	Scalp area	<i>16.4</i>	<i>40.5</i>

[a] Values in italics exceed the maximum skin adherence amount of 10 mg/cm² (Tibaldi et al. 2017). For subsequent exposure calculations, the skin surface application area was multiplied by 10 mg/cm² to determine mean and 95th percentile of product applied per skin surface area.

Table 3. Product-specific consumer exposure level (CEL) calculations for methyl-2-nonynoate

Product	Product Category ^[a]	Weight Fraction (%)	Retention Factor	Applications per day	Amount of product per application (mg/cm ²) ^[b]		CEL (µg/cm ² /day)	
					Mean	95th Percentile	Mean	95th Percentile
Lipstick	1 - Lip products	0.001	1	2.35	2.1	7.7	0.0490	0.1811
Solid antiperspirant	2 - Antiperspirants	0.001	1	1.3	4.7	10.0	0.0615	0.1300
Eye shadow	3 - Eye products	0.002	1	1.2	1.3	4.0	0.0300	0.0960
Body lotion	4 - Body lotions	0.002	1	0.97	0.3	0.6	0.0049	0.0114
Hair spray (aerosol)	4 - Hair sprays	0.002	0.1	1.49	3.2	9.3	0.0096	0.0276
Hair spray (pump)	4 - Hair sprays	0.002	0.1	1.51	4.6	10.0	0.0137	0.0302
Face cream	5 - Women's facial creams	0.002	1	1.77	3.6	8.7	0.1270	0.3092
Liquid foundation	5 - Women's facial make-up	0.002	1	1.24	1.6	5.0	0.0394	0.1240
Hair conditioner (leave-in)	8 - Leave-in hair conditioners	0.002	0.1	1.1	10.0	10.0	0.0220	0.0220
Shampoo	9 - Shampoos	0.002	0.01	1.11	10.0	10.0	0.0022	0.0022
Body wash	9 - Body washes	0.002	0.01	1.37	0.6	1.4	0.0002	0.0004
Facial cleanser	9 - Facial cleansers	0.002	0.01	1.6	7.6	10.0	0.0024	0.0032
Hair conditioner (rinse-off)	9 - Rinse-off conditioners	0.002	0.01	1.1	10.0	10.0	0.0022	0.0022

[a] Product categories from Api et al. (2008b) and IFRA

[b] See values in Table 2

Table 4. Product-specific margin of safety (MOS) calculations for methyl-2-nonynoate

Product	Product Type	CEL (µg/cm ² /day) ^[a]	SAF	MOS
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		NESIL ($\mu\text{g}/\text{cm}^2$)	Mean	95th Percentile		Mean	95th Percentile
Lipstick	Leave-on		0.0490	0.1811	300	1.6	0.4
Solid antiperspirant	Leave-on		0.0615	0.1300	300	1.3	0.6
Eye shadow	Leave-on		0.0300	0.0960	300	2.7	0.8
Body lotion	Leave-on		0.0049	0.0114	100	48.6	21.0
Hair spray (aerosol)	Leave-on		0.0096	0.0276	100	25.0	8.7
Hair spray (pump)	Leave-on		0.0137	0.0302	100	17.5	7.9
Face cream	Leave-on	24	0.1270	0.3092	100	1.9	0.8
Liquid foundation	Leave-on		0.0394	0.1240	100	6.1	1.9
Hair conditioner (leave-in)	Leave-on		0.0220	0.0220	100	10.9	10.9
Shampoo	Rinse-off		0.0022	0.0022	100	108.1	108.1
Body wash	Rinse-off		0.0002	0.0004	100	1372.0	638.0
Facial cleanser	Rinse-off		0.0024	0.0032	100	99.2	75.0
Hair conditioner (rinse-off)	Rinse-off		0.0022	0.0022	100	109.1	109.1

[a] See values from Table 3

Table 5. Product-specific margin of safety (MOS) values at mean and 95th percentile exposure scenarios for evaluated fragrance chemicals.

[REDACTED]

Product	[REDACTED]		[REDACTED]		[REDACTED]		[REDACTED]		[REDACTED]	
	Mean	95th	Mean	95th	Mean	95th	Mean	95th	Mean	95th
Lipstick	2.3	0.6	2.5	0.7	13.6	3.7	2.3	0.6	3.4	0.9
Solid antiperspirant	1.4	0.6	1.5	0.7	10.8	5.1	1.5	0.7	1.4	0.6
Eye shadow	1.1	0.3	1.2	0.4	4.4	1.4	1.5	0.5	1.4	0.4
Body lotion	20.2	8.8	8.9	3.9	81.0	35.0	8.9	3.9	20.2	8.8
Hair spray (aerosol)	10.4	3.6	4.6	1.6	41.6	14.5	4.6	1.6	10.4	3.6
Hair spray (pump)	7.3	3.3	3.2	1.5	29.1	13.2	3.2	1.5	7.3	3.3
Face cream	0.8	0.3	0.6	0.2	3.1	1.3	0.7	0.3	0.8	0.3
Liquid foundation	2.5	0.8	1.9	0.6	10.2	3.2	2.1	0.7	2.5	0.8
Hair conditioner (leave-on)	4.5	4.5	1.7	1.7	3.6	3.6	1.9	1.9	4.5	4.5
Shampoo	45.0	45.0	16.5	16.5	180.2	180.2	7.4	7.4	45.0	45.0
Body wash	571.7	265.8	209.6	97.5	2286.7	1063.4	93.8	43.6	571.7	265.8
Facial cleanser	41.3	31.3	15.2	11.5	165.4	125.0	6.8	5.1	41.3	31.3
Hair conditioner (rinse-off)	45.5	45.5	16.7	16.7	181.8	181.8	7.5	7.5	45.5	45.5

Product	[REDACTED]		[REDACTED]		[REDACTED]		[REDACTED]		[REDACTED]	
	Mean	95th	Mean	95th	Mean	95th	Mean	95th	Mean	95th
Lipstick	2.4	0.6	2.7	0.7	2.4	0.6	2.3	0.6	2.5	0.7
Solid antiperspirant	1.5	0.7	1.6	0.8	1.5	0.7	1.4	0.7	1.5	0.7
Eye shadow	1.5	0.5	1.5	0.5	1.5	0.5	1.5	0.5	1.5	0.5
Body lotion	8.8	3.8	9.0	3.9	9.0	3.9	8.9	3.9	9.0	3.9
Hair spray (aerosol)	4.5	1.6	4.6	1.6	4.6	1.6	4.6	1.6	4.6	1.6
Hair spray (pump)	3.2	1.4	3.2	1.5	3.2	1.5	3.2	1.5	3.2	1.5
Face cream	0.7	0.3	0.7	0.3	0.7	0.3	0.7	0.3	0.7	0.3
Liquid foundation	2.1	0.7	2.1	0.7	2.1	0.7	2.1	0.7	2.1	0.7
Hair conditioner (leave-on)	2.7	2.7	5.4	5.4	5.4	5.4	10.7	10.7	13.4	13.4
Shampoo	10.6	10.6	21.3	21.3	21.3	21.3	42.5	42.5	53.2	53.2
Body wash	134.9	62.7	269.8	125.5	269.8	125.5	539.7	251.0	674.6	313.7
Facial cleanser	9.8	7.4	19.5	14.8	19.5	14.8	39.0	29.5	48.8	36.9
Hair conditioner (rinse-off)	10.7	10.7	21.5	21.5	21.5	21.5	42.9	42.9	53.6	53.6

