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KATHON CG SKIN SENSITIZATION QUANTITATIVE RISK ASSESSMENT

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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 quantitative risk assessment of the skin sensitizing potential of daily exposure to Kathon CG, a preservative used in WEN's products, following use of various personal care and cosmetic products. This evaluation may inform the prioritization of product categories of concern and may provide guidance for potential future actions or additional safety testing.

Cardno ChemRisk calculated an estimated daily consumer exposure level (CEL) for rinse-off and leave-on products using the amount of product applied per application, number of applications per day, a retention factor, the Kathon CG concentration, and body surface area values. We compared estimated CELs to the no expected sensitization induction level (NESIL) for Kathon CG, and applied sensitization assessment factors to calculate product-specific margins of safety (MOS).

2. BACKGROUND

2.1 Background on Skin Sensitization

Skin sensitization is an immunological response caused by contact with an allergen that can result in the physical symptoms of allergic contact dermatitis (ACD). ACD develops in two stages: (1) the induction stage and (2) the elicitation stage. In the induction stage, a chemical, or skin sensitizer, reacts with skin proteins to form a conjugate. This initiates a cascade resulting in proliferation of allergen specific T-cells. In the elicitation stage, an individual is re-exposed to the same chemical triggering an immune response that leads to ACD (Gerberick and Robinson 2000).

Chemicals that cause skin sensitization typically react with skin proteins to induce allergenicity. Thus, there is a correlation between chemical protein reactivity and skin sensitization potential (Gerberick and Robinson 2000). In addition, it is known that the induction of skin sensitization is threshold-based, such that the likelihood is dependent upon the amount and frequency of dose per unit of skin area exposed (Gerberick, Robinson et al. 2001). Therefore, a key component of a risk assessment for skin sensitization is use of a benchmark value known as the no expected sensitization induction level (NESIL). A NESIL value is derived based on toxicology data for a given chemical and represents a level of exposure at which no skin sensitization is expected to occur. For the purposes on quantitative risk assessment, an expected consumer exposure level to a select ingredients is compared to the NESIL to determine the risk of skin sensitization under a given exposure scenario (Api, Basketter et al. 2008).

Damage to the hair can occur when personal care or cosmetic products are used incorrectly or too frequently, which may produce changes in hair texture that correspond to morphologic changes or even hair loss (Ahn and Lee 2002). Identified examples of such occurrences typically involve skin irritation and sensitization. For example, irritation to the skin may occur when irritants and

allergens from cosmetics, such as hair dye penetrate the scalp (Ishida, Makino et al. 2011; AlGhamdi and Moussa 2012). Alghamdi and Moussa (2012) reported that hair loss was a side effect among individuals who experienced skin irritation as a result of the use of hair dyes. In addition, hair highlighting has been shown to be able to cause allergic and irritant contact dermatitis resulting in hair loss (Lund, Unwala et al. 2010). Additionally, researchers have reported cases of inflammatory alopecia and allergic contact dermatitis following topical triggers, such as fragrances, sunscreens, as well as personal care and cosmetic products (Aldoori, Dobson et al. 2016; Admani, Goldenberg et al. 2017; Liu, Zimarowski et al. 2017). Goldenburg et al. (2017) noted that the "hallmark for contact alopecia is a preceding eczematous localized inflammatory response followed by hair loss, with notable regrowth of hair occurring by 6 months after allergen avoidance…[which is] consistent with contact-associated telogen effluvium" (Goldenberg, Admani et al. 2017, p. 626). Accordingly, based on the literature, hair loss caused by a cosmetic product would not be expected to occur without symptoms of irritation or sensitization.

2.2 Background on Kathon CG

Kathon is a proprietary name for a family of biocides and preservatives that contain active ingredients methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI) (de Groot and Weyland 1988). Specifically, Kathon CG is a cosmetic grade formulation that is widely used as a preservative in various personal care and cosmetic products. According to manufacturer documentation, the liquid Kathon CG product contains water and magnesium salts as inert ingredients, and 1.15% MCI (CAS: 26172-55-4) and 0.35% MI (CAS: 2682-20-4) as active ingredients (Dow 2006).

The Kathon CG preservative is used for its antimicrobial activity against gram-positive and gram-negative bacteria, molds, and yeast (Dow 2006). While beneficial, the active ingredients MCI and MI in Kathon CG have also been identified as strong skin sensitizers (Bruze, Gruvberger et al. 1987; Burnett, Bergfeld et al. 2010; Lundov, Krongaard et al. 2011). Given the widespread use of MCI and MI in personal care and cosmetic products, it is difficult to identify which products contribute the most to skin sensitization induction and contact allergy health effects observed across Europe and the United States (Urwin and Wilkinson 2013; Rothe, Ryan et al. 2017). Based upon safety evaluations, the CIR concluded that MCI/MI may be safely used in rinse-off products at a concentration up to 15 ppm and in leave-on products at a concentration up to 7.5 ppm, assuming that this mixture is 76.7% MCI and 23.3% MI (CIR (Cosmetic Ingredient Review) 1992). This equates to a final concentration of 0.1% and 0.05% Kathon CG in rinse-off and leave-on products, respectively.

2.3 Leave On/Rinse Off Definition

For their safety evaluations, the CIR distinguishes between leave-on and rinse-off products (such the WEN Products). They define a rinse-off product as one that is designed to be removed from the skin by rinsing (CIR, 1992). According to the European Union, a rinse-off product is a substance that is applied to the skin and/or hair system with the purposes of ‘‘cleaning them (toilet soaps, shower preparations, shampoos), to improve the condition of the hair (hair conditioning products) or to protect the epidermis and lubricate the hair before shaving (shaving products).’’

(EU, 2017). In contrast, leave-on products, such as body lotion, are applied to and left on the skin for an extended period. Based on safety evaluations, the CIR concluded that MCI/MI may be safely used in rinse-off products at a concentration up to 15 ppm and in leave-on products at a concentration up to 7.5 ppm, assuming that this mixture is 76.7% MCI and 23.3% MI (CIR, 1992). This equates to a final concentration of 0.1% and 0.05% Kathon CG in rinse-off and leave-on products, respectively.

3. METHODS

Products Containing MCI/MI

To better understand the prevalence of MCI and MI in consumer products, we queried two publicly-available databases (the National Library of Medicine's Household Products Database and the Environmental Working Group's Skin Deep Cosmetic Database) for all products that contained both MCI and MI. We searched the databases by chemical name and CAS number, and classified the results into the following personal care and cosmetic product categories: shampoos; conditioners; body washes, face washes, and exfoliants; makeup and fragrance; hair styling products; and lotions, creams, and moisturizers. We excluded products that contained just MCI or just MI.

MCI/MI Sensitization Risk Assessment

An estimated daily dermal exposure to MCI and MI among adult women following daily application of rinse-off and leave-on personal care and cosmetic products was calculated using 1) the amount of product applied per application, 2) the number of applications per day, 3) the MCI/MI concentration in the product, 4) a retention factor, and 5) the surface area of the body where the product was applied. Specifically, the consumer exposure level (CEL) associated with daily use of various personal care and cosmetic products was calculated using the following formula:

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

Where:

CEL: consumer exposure level (μg/cm^2/day)
MDE: product-specific maximum dermal exposure per application (μg/application)
A: product-specific mean number of applications per day (application/day)
RF: retention factor (the percent of product remaining on the skin)
C%: MCI/MI weight fraction (% weight/volume) in product
SA: surface area of body site where product is applied (cm^2)

A series of published consumer use practice studies have previously collected data on the amount of product applied and frequency of use of various personal care and cosmetic products (Loretz, Api et al. 2005; Loretz, Api et al. 2006; Loretz, Api et al. 2008). Specifically, 360 adult women (19-65 years old) from ten different regions in the United States recorded daily usage information for widely used products over a two-week long study period. These products included rinse-off products (shampoo, hair conditioner, body wash, and facial cleanser), as well as leave-on (body

lotion, face cream, liquid foundation, spray perfume, lipstick, eye shadow, and antiperspirant) products. We used product-specific data on the mean and 95th percentile amount of product applied per application and the mean number of applications per day. The adult female total body and body part-specific surface areas were determined from the Environmental Protection Agency (EPA) exposure factors handbook, scientific literature, and cosmetic safety evaluation guidance notes.

Based on recommended parameters for dermal exposure modeling, the maximum amount of liquid that can adhere to the surface of the skin is 10 mg/cm^2 (Tibaldi, ten Berge et al. 2017). Therefore, the maximum amount of applied product that could adhere to the skin per application was estimated using mean adult female site-specific body surface areas based on the location of product application. This value was used in exposure calculations if the mean or 95th percentile of applied amount exceeded the maximum possible amount of product that could adhere to the available skin area per application. Based on quantitative risk assessment technical guidance documents and literature, we applied a retention factor of 0.01 in rinse-off products and 1.0 in leave-in products (SCCS (Scientific Committee on Consumer Safety) 2016). This accounts for the generally accepted assumption that 100% of the leave-on product is left on the skin, while 1% of the rinse-off product remains on the skin as a residue following rinsing.

We assumed that the products contained the maximum recommended safe concentration of Kathon CG: 0.1% by weight in rinse-off products (15 ppm MCI/MI) and 0.05% by weight in leave-on products (7.5 ppm MCI/MI). The active ingredients MCI and MI compose 1.15% and 0.35% of Kathon CG, respectively, which equates to weight fractions of 1.15x10^{-5} (MCI) and 3.5x10^{-6} (MI) in rinse-off products and 5.75x10^{-6} (MCI) and 1.75x10^{-6} (MI) in leave-on products. Dermal studies have reported that 7 to 56% of MCI and MI in aqueous solutions have been absorbed across human skin over 24 hours (SCCS 2009). For this assessment, we conservatively assumed 100% absorption of MCI and MI in the calculations.

The calculated CELs were benchmarked to the weight-of-evidence (WoE) no expected sensitization induction level (NESIL) for a mixture of MCI and MI, which is the chemical-specific dose below which skin sensitization induction is not expected to occur. The Scientific Committee on Consumer Safety (SCCS) reported a NESIL of 0.83 µg/cm^2 for a MCI/MI mixture in a 3:1 ratio based on WoE data from human repeat insult patch tests (HRIPT) (SCCNFP 2003; SCCS 2015). A table summarizing HRIPT data, as reported by the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP), is shown in Table 1.

The acceptable exposure level (AEL) is the exposure per unit area that is not expected to induce skin sensitization in consumers, which is calculated by applying sensitization assessment factors (SAF) to the NESIL. SAFs are used to extrapolate information from a controlled exposure during the determination of a NESIL to an actual consumer exposure, by accounting for variation between subjects, matrices, and product use patterns (Api, Basketter et al. 2008; Rothe, Ryan et al. 2017). A margin of safety (MOS) was then calculated for Kathon CG for each product by dividing the AEL by the CEL. A margin of safety of one or greater indicates a low likelihood of sensitization induction.

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

[redacted]

Where:

MOS: margin of safety
AEL: acceptable exposure level (μg/cm^2/day)
NESIL: no expected sensitization level (μg/cm^2)
SAF: product-specific sensitization assessment factor
CEL: consumer exposure level (μg/cm^2/day)

The total SAF ranged from 100 to 300, based on reported skin sensitization quantitative risk assessment data for various personal care product types (lip products, shampoo, body wash/shower gels, etc.) (Api, Basketter et al. 2008). All products had a SAF of 10 for human variability (inter-individual variance), a SAF of 3 for matrix variability (product is a mixture that may not be the same as experimental conditions, may be designed to enhance penetration, and may contain irritating ingredients), and a SAF of 3 or 10 for use variability (body site may have increased permeability, include dry or abraded skin, have increased permeability, and be highly vascular with exposure to mucous membranes). Basketter and Safford 2016 proposed alternative SAF recommendations that were not product type-specific, but were based on inter-individual variance, matrix, frequency/duration of product use, occlusion, and skin condition factors (Basketter and Safford 2016). A sensitivity analysis determined that the study conclusions did not change when these alternative SAF recommendations were utilized.

4. RESULTS AND DISCUSSION

MCI and MI were identified in 2,082 consumer products across six product categories (Table 2). This included various brands of commonly used personal care and cosmetic products. Rinse-off products accounted for the majority (94%) of these personal care items, including shampoos (46%), conditioners (31%), and body/face washes (17%). MCI and MI were also identified ingredients in commonly used leave-on products, including lotions, hair styling products, and makeup products (Table 2).

The mean and 95th percentile amount of product applied per application (g) and the mean number of applications per use day are presented in Table 3. Lipstick had the smallest amount of product applied per application, while hair conditioner had the largest amount of product applied per application, for both the mean and 95th percentile exposure scenarios. The number of mean applications per day ranged from 0.97 (body lotion) to 2.35 (lipstick). Total and body part-specific (head, trunk, arms, hands, legs, and feet) surface areas for adult females (≥21 years old) were collected from the EPA's exposure factors handbook (EPA 2011). Additionally, Cadby et al. (2002) and Cowan-Ellsberry et al. (2008) reported surface areas of the scalp and axilla for adult females. We used adult female measurements from Ferrario et al. (2000) to calculate the lip surface area. The body surface areas for eye shadow and spray perfume products were taken from the SCCS guidance notes for cosmetic ingredient safety evaluations (SCCS (Scientific Committee on Consumer Safety) 2016). All surface areas used in product-specific risk assessments are reported in Table 3.

The amount of product applied per application, as reported in consumer use studies, exceeded the maximal dermal exposure threshold of 10 mg/cm^2 for shampoo and hair conditioner for the mean and 95th percentile exposure scenarios, as well as for antiperspirant and facial cleanser for the 95th percentile exposure scenarios. Therefore, the maximum amount of product that could adhere to the available skin area, based on the location of application, was used in the CEL calculations for these products. All parameters used in product-specific CEL calculations are shown in Table 4.

The CELs ranged from 1.3x10^{-4} µg/cm^2/day (body wash) to 1.7x10^{-3} µg/cm^2/day (shampoo and hair conditioner) for rinse-off products, while the CELs ranged from 1.9x10^{-3} µg/cm^2/day (body lotion) to 0.12 µg/cm^2/day (spray perfume) for leave-on products (Table 4). All calculated CELs were lower than the reported MCI/MI NESIL of 0.83 µg/cm^2. All MOSs for rinse-off products (shampoo, conditioner, body wash, and facial cleanser) were above 1.0 (unlikely to induce skin sensitization) for both the mean and 95th percentile exposure scenarios. In contrast, after applying product-specific SAF, all MOSs for leave-on products (lipstick, body lotion, face cream, liquid foundation, antiperspirant, spray perfume, and eye shadow) were below 1.0 for both the mean and 95th percentile exposure scenarios, except for the mean exposure model for body lotion. Specifically, the MOSs for rinse-off products ranged from 5 (shampoo) to 63 (body wash), while the MOSs for leave-on products ranged from 0.02 (antiperspirant) to 1.49 (body lotion) (Table 5).

This analysis performed a quantitative risk assessment of the potential of MCI/MI (active ingredients in a commonly used cosmetic product preservative Kathon CG) to induce skin sensitization among adult female consumers. Specifically, we examined the sensitization induction potential of various rinse-off and leave-on personal care and cosmetic products containing the maximum recommended safe concentration of MCI and MI in Kathon CG, with our results providing evidence that the product type is an important driver of skin sensitization induction. Overall, our analysis indicates that rinse-off products (e.g. shampoo) are not expected to induce sensitization, while prolonged dermal contact with leave-on products (e.g. face cream) may result in an increased risk of sensitization induction among consumers.

All MOSs for rinse-off products (shampoo, hair conditioner, body wash, and facial cleanser) containing the maximum recommended safe concentration of 15 ppm MCI/MI were greater than 1.0 for all products under both the mean and 95th percentile exposure scenarios, indicating a low likelihood of sensitization induction. Our findings suggest that the current recommended safe concentration of MCI/MI in rinse-off products is highly conservative and that a higher level of MCI/MI may be allowable in rinse-off products without increasing the likelihood of sensitization induction.

For leave-on products (body lotion, lipstick, face cream, antiperspirant, spray perfume, and eye shadow) containing the maximum recommended safe concentration of 7.5 ppm MCI/MI, all MOSs were below 1.0 for either the mean or 95th percentile exposure model, indicating an increased risk of sensitization induction. In contrast to our rinse-off findings, these results suggest that the current recommended safe concentration of MCI/MI in leave-on products could induce sensitization in some use scenarios, and that a lower concentration of MCI/MI may be necessary for leave-on products. Our findings suggest that the skin sensitization induction to MCI/MI is more likely due to leave-on products rather than rinse-off products.

This quantitative risk assessment demonstrates the importance of considering the product type, the concentration of preservatives, and the application surface area when assessing the risk of sensitization induction.

5. CONCLUSIONS

Cardno ChemRisk performed a quantitative risk assessment of the skin sensitizing potential of Kathon CG present in the WEN Products.

Our results provide evidence that certain leave-on products containing the maximum recommended safe concentration of Kathon CG may increase the risk of the induction of sensitization due to exposure to MCI/MI. In contrast, rinse-off products were not associated with a potential increased risk of skin sensitization induction. Specifically, these results indicate that use of the WEN Products, which are rinsed off of the scalp, would not be associated with an increased risk of skin sensitization induction due to exposure to MCI/MI.

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Table 1. Human Repeat Insult Patch Test data for MCI/MI, as reported by the SCCNFP

Dose (MCI/MI [3:1]) (µg/cm^2)	**Incidence (Sensitization)**	**% Response**
0.42	0/416	0
0.5	0/103	0
0.75	0/184	0
0.83	0/602	0
1.04	1/84	1.2
1.25	0/200	0
1.34	2/189	1.1
1.67	2/45	4.4
2.5	0/109	0
5	5/116	4.3
7.5	7/196	3.6

[redacted]

Table 2. Number of products identified to contain MCI and MI

Product Category	**N Containing MCI and MI (%)**
Shampoo	960 (46.1%)
Conditioner	644 (30.9%)
Body Wash, Face Wash, and Exfoliant	362 (17.4%)
Lotions, Creams, and Moisturizers	40 (1.9%)
Hair Styling Products	66 (3.2%)
Makeup and Fragrance	10 (0.5%)
Total	2082

Table 3. Amount of product applied per application per consumer use data surveys and adult female skin area for site of product application

Product	Product Type	Amount applied per application (g)		Mean Number of Applications per Day	Source	Skin Surface Area (cm^2)	Notes	Source
		Mean	95th Percentile					
Lipstick	Leave-on	0.01	0.037	2.35	Loretz 2005	19	Mouth width x total lip height	Ferrario et al. 2002
Body lotion	Leave-on	4.42	10.22	0.97	Loretz 2005	17360	Total body area - head area	EPA 2011
Face cream	Leave-on	1.22	2.97	1.77	Loretz 2005	340	Head area - scalp area	EPA 2011; Cadby et al. 2002
Liquid foundation	Leave-on	0.54	1.7	1.24	Loretz 2006	340	Head area - scalp area	EPA 2011; Cadby et al. 2002
Antiperspirant	Leave-on	0.61	1.67	1.3	Loretz 2006	129	Axilla area x2	Cowan-Ellsberry et al. 2008
Eye shadow	Leave-on	0.03	0.096	1.2	Loretz 2008	24	Eye shadow area	SCCS 2016
Spray perfume	Leave-on	0.33	0.94	1.67	Loretz 2006	100	Spray perfume area	SCCS 2016
Shampoo	Rinse-off	11.76	27.95	1.11	Loretz 2006	800	Scalp area	Cadby et al. 2002
Body wash	Rinse-off	11.3	24.3	1.37	Loretz 2006	17700	Total body area - scalp area	EPA 2011; Cadby et al. 2002
Facial cleanser	Rinse-off	2.57	5.89	1.6	Loretz 2008	340	Head area - scalp area	EPA 2011; Cadby et al. 2002
Hair conditioner	Rinse-off	13.13	32.43	1.1	Loretz 2008	800	Scalp area	Cadby et al. 2002

Table 4. Parameters used to calculate consumer exposure levels (CEL)

Product	Classification	Weight Fraction MCI/MI	Retention Factor	Applications/ Day	MDE per application (µg)		Surface Area (cm^2)	CEL (µg/cm^2/day)	
					Mean	95th Percentile		Mean	95th Percentile
Lipstick	Leave-on	0.0000075	1	2.35	10000	37000	19	0.0093	0.0343
Body lotion	Leave-on	0.0000075	1	0.97	4420000	10220000	17360	0.0019	0.0043
Face cream	Leave-on	0.0000075	1	1.77	1220000	2970000	340	0.0270	0.0657
Liquid foundation	Leave-on	0.0000075	1	1.24	540000	1700000	340	0.0084	0.0264
Antiperspirant	Leave-on	0.0000075	1	1.3	610000	1290000[a]	129	0.0461	0.0975
Eye shadow	Leave-on	0.0000075	1	1.2	30000	96000	24	0.0113	0.0360
Spray perfume	Leave-on	0.0000075	1	1.67	330000	940000	100	0.0413	0.1177
Shampoo	Rinse-off	0.000015	0.01	1.11	800000[a]	800000[a]	800	0.0017	0.0017
Body wash	Rinse-off	0.000015	0.01	1.37	11300000	24300000	17700	0.0001	0.0003
Facial cleanser	Rinse-off	0.000015	0.01	1.6	2570000	3400000[a]	340	0.0010	0.0014
Hair conditioner	Rinse-off	0.000015	0.01	1.1	8000000[a]	800000[a]	800	0.0017	0.0017

[a] Amount applied per application exceeded the maximal dermal exposure (10 mg/cm2), so the maximal dermal exposure based on available skin surface area at location of application was used

MDE = maximal dermal exposure

CEL = consumer exposure level

Table 5: Skin sensitization induction margins of safety (MOSs) by product

Product	Classification	NESIL ($\mu g/cm^2$)	SAF	MOS	
				Mean	95th Percentile
Lipstick	Leave-on	0.83	300	0.29	0.08
Body lotion	Leave-on		300	1.49	0.65
Face cream	Leave-on		100	0.31	0.13
Liquid foundation	Leave-on		100	0.99	0.31
Antiperspirant	Leave-on		300	0.06	0.03
Eye shadow	Leave-on		300	0.25	0.08
Spray perfume	Leave-on		100	0.20	0.07
Shampoo	Rinse-off		100	4.98	4.98
Body wash	Rinse-off		100	63.26	29.42
Facial cleanser	Rinse-off		100	8.07	6.10
Hair conditioner	Rinse-off		100	5.03	5.03

NESIL: no expected sensitization induction level
SAF: sensitization assessment factor
MOS: margin of safety