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ADVERSE EVENT RATE COMPARISON: WEN RATES VERSUS BACKGROUND RATES

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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 reviewed the background rate for the general public's allergenic response to cosmetic products generally and compared that to the complaint rate for the WEN Products.

Individuals react to cosmetic and personal care products at some background rate. However, quantification of the exact background response is challenging. Consumers typically do not seek medical treatment, or discontinue use of the products, if a mild reaction occurs (Mehta and Reddy, 2003; cited by Park and Zippin, 2014). Databases and other sources of medical reporting are likely to underestimate actual incidence. Therefore, predictions of the incidence or prevalence of cosmetic or personal care product allergy and irritation in the general population are highly uncertain and likely lower than the actual response rate.

With that being said, there have been studies performed on the background response rate to exposure to cosmetic products that can be used to develop an estimate for the background response rate to exposure to cosmetic products. To date, most analyses of cosmetic or personal care product-related allergies were conducted in populations of dermatological patients; i.e., a sensitive subpopulation of people with skin conditions that seek treatment. Approximately 8-10% of dermatological patients had a positive cosmetics patch test (Romaguera et al., 1983; Biebl and Warshaw, 2006). Of those patients, approximately 40% had developed contact dermatitis (Romaguera et al., 1983). Approximately 24% of female and 18% of male patients with suspected allergic contact dermatitis (ACD) developed an allergic reaction to cosmetics (Warshaw et al., 2009; cited by Park and Zippin, 2014). Overall, these studies estimate that approximately 0.5 - 1% of the total general population has a contact allergy to cosmetics and personal care products (Biebl and Warshaw, 2006; Park and Zippin, 2014). However, these estimates are likely an under prediction, due to lack of reporting for mild reactions and reliance on sensitive subpopulations.

Some ingredients used in cosmetics and personal care products are tied to higher levels of allergy in the general population. For example, approximately 3-4% of the general population is expected to be allergic to fragrances (Peiser et al., 2012; Alinaghi et al., 2019). Pooled prevalence analysis also predicts that 1.5% of the general population is allergic to the preservative methylchlorisothiazolinone/methylisothiazolinone (Kathon CG) (Alinaghi et al., 2019). ACD on the scalp is generally attributed to hair coloring agents, but some reviews have indicated that hair-cleansing products may also contribute to scalp ACD (Hillen et al. 2007; cited by Park and Zippin, 2014).

There is a possibility that polysensitization, or sensitization to multiple allergens, may increase the severity of allergic reactions and increase the likelihood of a reaction to a "weak" allergen (Peiser et al., 2012; citing Brasch et al. 2006 and Schunch et al. 2007). Further analysis of the

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collected case reports, or prospective capture of personal allergy status in the adverse event reports, could determine if severe outcomes are more likely to occur in polysensitized individuals (i.e., women who use sensitizing hair dyes, or people with fragrance allergy). WEN marketing information could also be used to identify potentially relevant co-correlated population attributes that may not be captured in the adverse event databases. For example, information on the typical WEN consumer (i.e., regional, socioeconomic, or age-based marketing) could identify populations with characteristics that may lead to susceptibility or polysensitization.

The experience of WEN users should be considered in the context of general background rates of skin and hair disorders. This is especially important here because, after reviewing the scientific literature, we have concluded that hair loss caused by a topical hair cleansing product most likely will involve skin irritation or sensitization resulting from allergenic contact dermatitis. 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). Researchers have also 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). As a result, comparing the complaint rate of hair loss for the WEN Products with the general rate of contact allergy in the general population is useful in assessing whether the WEN Products presents a risk to consumers. If the complaint rate for the WEN Products is higher than the general rate of contact allergy in the general population, then it likely represents a risk to consumers. And, the reverse is true—if the complaint rate for the WEN Products is significantly lower than the general rate of contact allergy in the general population, then it likely is not a risk to consumers.

Overall, the prevalence of contact allergy in the general population is high. Approximately 15-20% of the general population is estimated to have contact allergy, with consumer products being identified as one of the risk factors (Peiser et al., 2012; Alinaghi et al., 2019). Adult women (i.e., between 20-55 years of age) have the highest prevalence of contact dermatitis (Peiser et al., 2012). Irritant dermatitis is expected to be more common than ACD (Park and Zippin, 2014; Emmons and Marks 1985, as cited by Biebl and Warshaw 2006) since it generally precedes allergic dermatitis (Peiser et al., 2012). However, Peiser et al., (2012) estimate that only 10% of the population has irritant contact dermatitis. These high background rates of idiopathic or multi-faceted skin disorders makes isolating effects to one product or ingredient difficult, unless the product-specific incidence is extremely high.

Screening analyses of the WEN Products show that all ingredients are commonly used in other personal care and cosmetic products (Fung et al., 2018). It is possible that the reported effects of skin irritancy, hair loss, and allergic contact dermatitis are not unique to the WEN Products but occur at some background rate for all personal care products. Therefore, this analysis compared the experience of the WEN Product users to various background rates, based on incident reporting and product sales data.

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2. METHODS

The FDA Center for Food Safety and Applied Nutrition (CFSAN) maintains the Adverse Event Reporting System (CAERS) database, which contains information on adverse events reported to the FDA by consumers, physicians, and health practitioners. The CAERS database contains product complaint reports for foods, dietary supplements, and cosmetics, and includes data for minor to major medical events, as well as complaints regarding non-medical issues, such as product taste, color, and packaging.

Publicly available data were extracted from the FDA CAERS database from January 2004 to March 2019. Data were restricted to reports that included the WEN Products or references to Chaz Dean in product names and were further limited to potential hair cleansing products, including conditioner, cleansing, shampoo, hair care system, and unspecified WEN products. The following products were excluded from the analysis: re-moist mask/hair treatment, hair mask, moisturizer/lotion, sprays/mists, pastes/creams, mousse/foam, treatment oil, hair gel, toners, smoothing gloss, anti-frizz, texture bomb, and volumizing treatment.

Reports may include the specific date that the event occurred, but if this data was not included in the report, it was assumed that the event occurred on the date that the CAERS report was submitted. Daily data were summed to include adverse event frequency data for each month for each year (e.g. October 2005). If no adverse events were reported in a specific month, that month was assigned a value of 0. Based on the available WEN Products sales records, a subset of adverse event data (January 2005 to December 2018) were evaluated in this analysis. For the sales data, monthly totals for each year were available for 2016 to 2018, but only yearly totals were available for 2005 to 2015. Therefore, the monthly distribution from the available data was applied to the yearly-only data to estimate monthly totals; however, this assumes that the monthly distribution from 2016 to 2018 was similar to the 2005 to 2015.Monthly adverse event rates were calculated by dividing the number of adverse event reports involving the WEN Products by the number of units sold of the WEN Products for each month over the 2005 to 2015 time period. This assumed that each unit of the WEN Products sold represented a unique customer.

In addition, we compared the number of hair loss complaints that the FDA publicly reported were directly received by the two companies (WCD and Guthy-Renker, LLC ("GR") who distributed the WEN Products between 2005 and 2016) plus the total number of adverse event reports in the CAERS database with the total number of unique customers between November 1, 2007 and September 19, 2016 reported in filings by the class action plaintiffs in the lawsuit entitled *Friedman, et al. v. Guthy-Renker, LLC, et al.*, U.S.D.C. Central District of California Case No. 2:14-CV-06009-ODW-AGR (the "Class Action").

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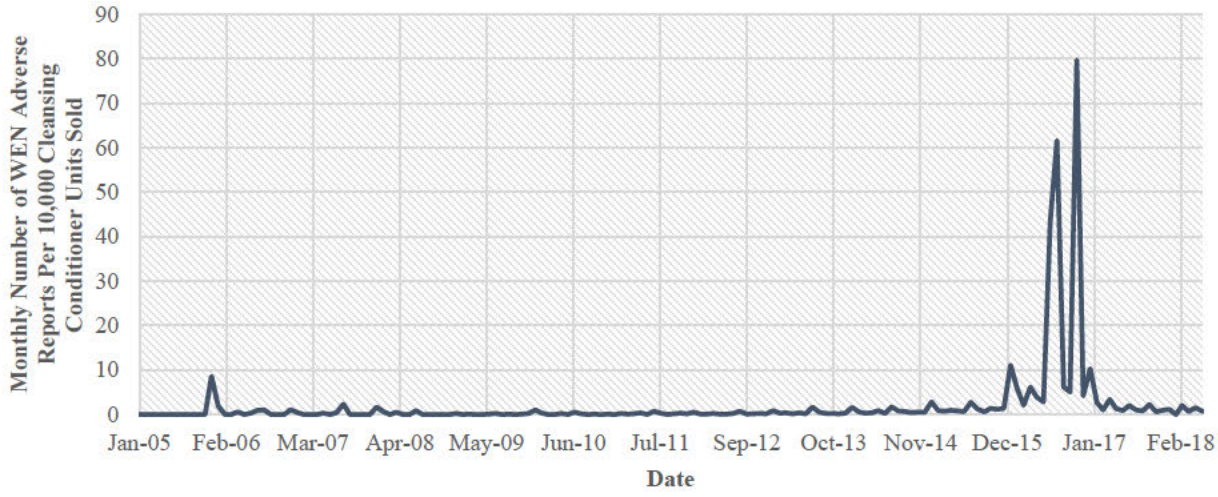
3. RESULTS

A total of 1,997 adverse events were reported between January 2005 and December 2018 among the products that fit the study inclusion criteria. The most commonly reported adverse events were alopecia (88.9%), pruritus (21.5%), and trichorrhexis (14.8%), but various other outcomes were reported, including rash/dermatitis, irritation, burning, hypersensitivity, and abnormal hair growth/texture. There was a sharp increase in the number of adverse event reports in 2015 and 2016 (Figure 1). During the 2015 to 2016 time period, there was also an observed increased in the number of WEN adverse events per number of units sold (Figure 2). The rate of all reported WEN cleansing conditioner-specific adverse events ranged from 0% to 0.80% of sales over the analyzed time period (Figure 2).



cleansing conditioner units sold, over the 2005 to 2018 time period.

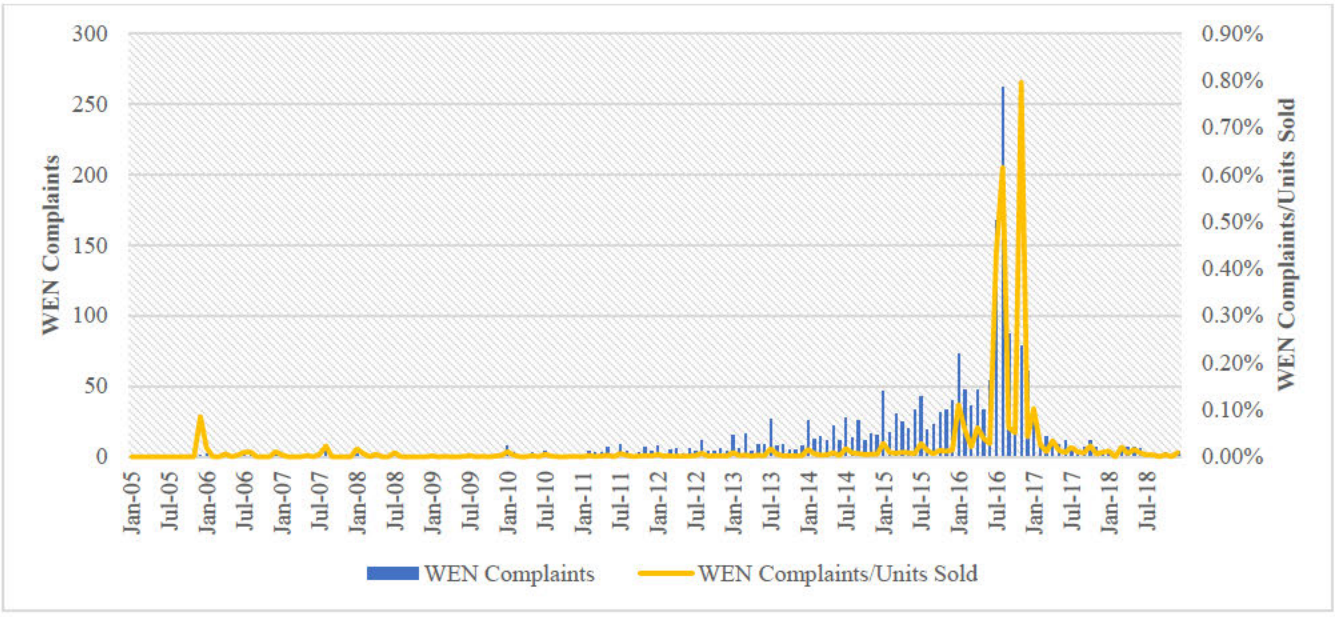


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Figure 2. Monthly total of WEN cleansing conditioner complaints in the FDA CAERS database and the rate of WEN cleansing conditioner adverse event reports per cleansing conditioner units sold, over the 2005 to 2018 time period.

As to the comparison of the number of hair loss complaints that the FDA reported were received by the companies with the number of unique customers reported in the Class Action, that complaint rate is 0.27%, utilizing the maximum numbers of reported complaints. In various public statements, the FDA reported that the companies had received 21,000 complaints. 1,997 adverse event reports were identified in the CAERS database for 2005 through December 2018. Those two numbers total 22,997. We have been informed that over 8,250,000 unique customers were sent notice of the settlement in the Class Action (which does not include customers whose emails or contact information were not known). Based on these numbers, the complaint rate versus unique customers is 0.27%.

4. CONCLUSIONS

As reported above, background rates have been estimated to be 10% for irritant contact dermatitis, 15-20% for contact allergy (general population), and 1% for contact allergy related to cosmetic and personal care use. In comparison, the monthly rate of adverse events among users of the WEN Products was estimated to be 0% to 0.8%, based on adverse event reporting from the FDA CAERS database and available sales data. This rate is consistent with the background rate of contact allergy related to personal care and cosmetic product use. It should also be noted that this rate of up to 0.8% includes all types of adverse events and is not specific to just contact allergy. Furthermore, the 0.25% complaint rate for unique users of the WEN Products is significantly lower than the background rates for contact allergy in the general population and cosmetic and personal care products.

It should also be noted that a temporal spike in adverse event reporting was observed in 2015 and 2016, which resulted in the upper bound estimate of 0.8%. Research has provided evidence that adverse event reporting may be related to factors unrelated to product use, such as media reporting and litigation. Therefore, it is important to note that both media events and litigation filings happened during the 2015 and 2016 time period, which may have influenced reporting behaviors. It may be possible that the adverse event rate for WEN users may be lower, if these external events were associated with reporting bias that resulted in overreporting.

In conclusion, analysis of WEN-specific sales data provides evidence that the adverse event experience of WEN users is not different from the background adverse event experience among users of personal care and cosmetic products, and analysis of the WEN-specific unique users data is significantly less than the background adverse event experience among users of personal care and cosmetic products. Accordingly, the complaints submitted to WCD and GR and the CAERS system do not support the premise that the WEN Products cause any adverse events, including hair loss. Indeed, based on the comprehensive risk and safety assessment we performed on the WEN Products, they are safe.

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