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PRELIMINARY *IN SILICO* SKIN IRRITATION AND SENSITIZATION ASSESSMENT

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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 engaged in several tests to assess the skin irritation and sensitization potential of the WEN Products, which, according to a review of the scientific literature, can lead to hair loss in some individuals. One such test we performed on the WEN Products was an *in silico* evaluation of the skin irritation and skin sensitization potential of the ingredients in several versions of the WEN ingredients. This screening level assessment may inform the prioritization of chemicals of concern and may provide guidance for potential future actions.

To perform this analysis, we used the profilers in the toolbox created by the Organisation for Economic Co-operation and Development (OECD). The OECD is an international respected intergovernmental economic organization that provides its members with a forum and a platform to compare policy experiences, seek answers to common problems, identify good practices and coordinate domestic international policies of its members which publishes guidelines for various industries on good practices. The OECD Toolbox is a software application intended to be used by governments, chemical industry and other stakeholders in filling gaps in toxicity data needed for assessing the hazards of chemicals. The OECD toolbox was used to determine structural alerts for any ingredients in the WEN Products. This type of assessment is widely practiced in academia, industry, and government agencies throughout the world and is a growing area of research (Cherkasov et al. 2014). However, there are limitations to the predictive power of all computer models. For example, computer models cannot analyze mixtures and do not consider dose. There are no computer models that are able to perfectly predict toxicity based on chemical structures, but, this tool is informative and can be used to make decisions and reduce the use of resources (e.g., animals).

2. BACKGROUND

2.1 Background on Skin Irritation and Skin Sensitization

- Skin Irritation

In animal experiments, dermal irritation has been defined as "the production of reversible damage of the skin following the application of a test substance for up to 4 hours" (OECD 404). Erythema (redness), eschar (scabs) and edema (swelling) are common manifestations of dermal irritation (Gallegos Saliner et al. 2007). At times, additional symptoms may occur, like small areas of alopecia, hyperkeratosis, hyperplasia and scaling. The standard test for assessing skin irritation is the Draize rabbit skin test (Gallegos Saliner et al. 2007). The underlying mechanisms of skin

irritation are diverse and not well understood but a few fundamental physicochemical properties have been identified (Gallegos Saliner et al. 2007).

The profilers of skin irritation rely on the basic physicochemical properties that underlie the irritant response. These properties include: the fundamental acidic and basic properties of the chemical, its ability to penetrate the skin (a function of hydrophobicity and molecular size), and cytotoxicity (Gallegos Saliner et al. 2007). Thus, certain parameters may be used to define cut-offs (e.g. a range of pH values, or molecular weights) so that compounds with a physicochemical parameter below or above a certain value can be classified as toxic (or non-toxic) (Gallegos Saliner et al. 2007).

- 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 et al. 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 et al. 2000). There are computer models that use structural moieties associated with protein reactivity to predict skin sensitization.

No models are able to perfectly predict skin irritation or skin sensitization based on chemical structure alone. For example, a chemical containing a chemical moiety that causes a structural alert does not mean it is a skin sensitizer as skin permeability or the position of moiety may reduce the potential for reaction. The converse is also true, in that, not having a positive prediction does not eliminate the possibility that a chemical is a skin sensitizer (Gerberick et al. 2000). Rather, the in silico models are helpful in guiding prioritization of future testing or formulations. In comparison to experimental data, a large number of chemicals can be evaluated at one time with less resources (animals, time, and cost).

- Links to Hair Loss

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). 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). 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.

3. METHODOLOGY

In order to determine ingredients that had a defined chemical structure appropriate for *in silico* analysis, the Chemical Abstracts Service (CAS) numbers were searched in PubChem and the Simplified Molecular Input Line Entry System (SMILES) string was identified. Thirty-five ingredients were identified in this manner and are shown in Table 1. The chemicals were profiled in the OECD toolbox (version 4.0.0.26167). The toolbox contains profilers that relate the chemical to a previously defined category, mode of action, or metabolite. Two profiles were run for skin irritation: skin irritation/corrosion exclusion rules by the German Federal Institute for Risk Assessment (BfR) and skin irritation/corrosion inclusion rules by BfR. Five profiles were run for skin sensitization: protein binding alerts for skin sensitization, protein binding by Oasis v1.4, protein binding by OECD, protein binding potency, protein binding potency Cys (DPRA 13%), and protein binding potency Lys (DPRA 13%). Details for each of the profilers are discussed below. No Quantitative Structure Activity Relationships (QSAR) analysis was run for the ingredients.

- Skin Irritation Profilers

The exclusion rules for skin irritation/corrosion are based on physicochemical cut-off values to identify chemicals that do not exhibit skin irritation or corrosion potential. The parameters used for defining skin irritation rules are: lipid solubility, surface tension, octanol water partition coefficient, vapor pressure, aqueous solubility, melting point, and molecular weight. If one of the rules applies to a substance it is predicted to be very unlikely that the substance can give effects in the standard test for skin irritants (OECD 404) that would lead to classification of the substance as an irritant or corrosive. It has been noted that some of the physicochemical properties have limited predictive value (e.g., lipid solubility, as it is not a generally available physical property) (OECD 2017).

Skin irritation/corrosion inclusion rules are structural alerts that can be used for positive classification of chemicals causing irritation/corrosion. There are 40 structural fragments that predict skin irritation/corrosion (OECD 2017).

- Skin Sensitization Profilers

The protein binding alert for skin sensitization was developed to investigate the presence of alerts within the target molecules that interact with proteins. The profiler accounts for the incapability of some chemicals that have an alert to interact with skin due electronic and steric factors. There are around 100 alerts in 11 mechanistic domains (OECD 2017).

The protein binding alert by OASIS v1.4 is to investigate alerts within target molecules responsible for interaction with proteins. There are 101 structural alerts in 11 mechanistic domains. There is a disclaimer within this profiler that states that the chemical functionalities that may interact with proteins from a theoretical point of view; they are not considered SARs (OECD 2017).

The profiler of protein binding by OECD was developed by an analysis of direct acting structural alerts based on theoretical organic chemistry. There are 52 structural alerts in 16 mechanistic categories (OECD 2017).

The protein binding potency profiler was developed based on empirical data for thiol reactivity. The profiler measures the target chemical's covalent binding with the thiol group of glutathione via SN2 reaction or Michael addition. Target chemicals are classified in their potency of reaction with glutathione (extremely, highly, moderately, slightly, and suspect) (OECD 2017).

The protein binding potency Cys/Lys is based on data derived from Direct Peptide Reactivity Assay (DPRA). DPRA evaluates the ability of a chemical to react with cysteine and lysine. The reactivity of the protein is measures by percent peptide depletion. The set of 77 structural alerts are separated into three categories DPRA above 21%, DPRA less than 9%, and Grey zone 9-21%.

4. RESULTS AND DISCUSSION

Thirty-five ingredients were run through the OECD toolbox profilers described above. Since some of the chemicals have limited or no experimental data, it is informative from a screening level perspective to apply computer modeling programs. The results for the OECD profilers are reported in Table 1.

- Skin Irritation

The skin irritation/corrosion exclusion rules by BfR resulted in a "(undefined)" for lipid solubility for all 35 ingredients. For all of the ingredients there is no experimental data for lipid solubility and the property cannot be used to determine if the chemicals are within the cut-off values. It appears that none of the other exclusion rules are met, thus, none of the chemicals are predicted to not be an irritant based on physiochemical cut-off values.

For the skin irritation inclusion rules, all but five of the chemicals did not meet the inclusion rules. That is, for 30 of the chemicals, there was no alert that the chemical would cause irritation/corrosion. Thus, the majority of the chemicals met neither the inclusion or exclusion rules for skin irritation.

Five chemicals had a structural alert for skin irritation/corrosion by the inclusion rules (Table 1).

- Behentrimonium methosulfate had a structural alert for esters of organic sulfonic or sulfuric esters. There were no data available on the dermal irritation of behentrimonium methosulfate. A three minute exposure of rabbits to a 5% solution of behentrimonium chloride did not cause any skin irritation (Becker et al. 2012). Transient erythema was observed in rabbits one hour after exposure to behentrimonium chloride concentrations of

7.7 to 8.3%, which resolved by 72 hours (Becker et al. 2012). Other members of the trimonium family have exhibited irritation at concentrations greater than 20% in several animal studies (Becker et al. 2012). The dermal absorption of other straight or branched chain alkyl trimonium ingredients was reported to be equal to or less than 3% (Becker et al. 2012). Behentrimonium methosulfate is in over 270 personal care products, primarily hair conditioning products, at concentrations that range from 0.1 to 10% (Becker et al. 2012). A CIR expert panel concluded that it was safe in the present practice of use and concentration.

- Dicetyldimonium chloride had a structural alert for quaternary organic ammonium. There is no available experimental information in animals or humans on the irritation potential of this ingredient. This ingredient is classified as a surfactant, conditioning agent, emulsifier, and antistatic agent for cosmetic use (ChemIDPlus 1812-53-9).
- Phenoxyethanol had a structural alert for ethylenglycoethers. However, multiple clinical human studies reported that no irritation occurred in subjects exposed up to 15% phenoxyethanol (Scognamiglio et al. 2012). Slight to moderate irritation was observed in animals administered 100% phenoxyethanol (Scognamiglio et al. 2012). Phenoxyethanol is used as fragrance ingredient in multiple cosmetic products including shampoos and soaps.
- Tocopherol had a structural alert for phenols. Tocopherol is not considered to be a skin irritant in human clinical studies (CIR 2014b). Patch-testing was performed with tocopherol, at an unspecified concentration, in 1,136 patients between1987 and 1997 (CIR 2014b). Six patients or 0.53% had a positive reaction to the patch-test. A similar incidence rate, 0.66%, was reported in a total of 1,814 patients tested between 1998 and 2007 (CIR 2014b). Alpha-tocopherol was applied for 48 hours by the North American Contact Dermatitis Group from 1994 to 2006 (CIR 2014b). The frequency of positive patch-tests varied over time from 0.5% to 1.1% (CIR 2014b). Tocopherols are used extensively as an antioxidant and skin conditioning agent in cosmetics products including lotions, oils, creams, powders, make-up and hair- or deodorant spray products (CIR 2014b). The maximum concentration of tocopherol in leave-on products in 2015 was 5.4% (CIR 2014b).
- Vanillin had an alert for aldehydes. Skin irritation studies evaluating vanillin conducted in rabbits and guinea pigs reported negative results (OECD 1996). In humans, patch tests of vanillin at doses ranging between 2% and 20% in normal subjects, and 0.4% in subjects with dermatitis showed no primary irritation (Opdyke 1977; OECD 1996). Vanillin is used in cosmetic including perfumes, creams, and lotions. Normal concentrations as an ingredient in perfumes is 0.2% with a maximum of 0.8%, while significantly less is found in creams and lotions, 0.005% normal and 0.03% maximum (OECD 1996).

For the five chemicals with structural alerts for skin irritation, four have some empirical data or data from the same family on skin irritation. Experimental data is considered more reliable than

the *in silico* predictions. Dicetyldimonium chloride had no *in vivo* experimental data. It is interesting to note that all five ingredients with a structural alert are commonly used in cosmetics.

- Skin Sensitization

A skin sensitizer is an agent that may cause an allergic response in susceptible individuals. Eight chemicals had an alert in at least one of the skin sensitization profilers.

- Methylchloroisothiazolinone and methylisothiazolinone had an alert in all or almost all of the categories related to skin sensitization. Both chemicals had alerts for SN2 reactions, were moderately reactive with glutathione, and reactive with cysteine. Only methylchloroisothiazolinone was predicted to be reactive with lysine. These chemicals make up the preservative Kathon CG. Kathon CG may cause contact dermatitis (skin irritation and/or skin sensitization) at concentrations higher than the recommended use level (Rohm&Haas 2007). Kathon CG was reported to be a potential sensitizer in a number of human and animal studies (Chan et al. 1983; Maibach 1985; de Groot et al. 1988; SCCS 2009; Potter et al. 1995). However, Kathon CG is a common preservative in personal care products.
- Panthenol had a single alert for acylation. Skin sensitization clinical studies conducted with products that contained panthenol concentrations ranging from 0.1 to 0.5% all reported that panthenol had no potential for allergic sensitization (Johnson 1987). However, a few cases of allergic contact dermatitis resulting from the use of cosmetic products containing 0.5% to 75% panthenol have been reported (Roberts et al. 2006; Chin et al. 2013; Stables et al. 1998). Panethol is used as an emollient in hair conditioners (Johnson 1987).
- Stearamidopropyl dimethylamine had a single alert for acylation. For stearamidopropyl, contact sensitization was generally not reported with hair conditioners containing up to 2% stearamidopropyl dimethylamine (CIR 2014a). The ingredient is used in rinse off product including hair conditioners as an antistatic and conditioning agent at concentrations of 0.011-5% (CIR 2014a).
- Pelargonium Graveolens Oil (the structure associated with the CAS number) had a structural alert in three of the models for Michael Addition and was predicted to be moderately reactive with glutathione. We are not aware of skin sensitization studies on this ingredient. This ingredient is contained in other personal care products.
- PCA and sodium PCA had an alert in two of the models for acylation. We are not aware of skin sensitization studies on this ingredient. This ingredient is contained in other personal care products.
- Hydrolyzed rice protein (the structure associated with the CAS number) had a single alert for Schiff base formation. We are not aware of skin sensitization studies on this ingredient. This ingredient is contained in other personal care products.

For the eight chemicals with structural alerts for skin sensitization, four have some empirical data. Experimental data is considered more reliable than the predictions. It is interesting to note that all five ingredients with a structural alert are commonly used in cosmetics.

5. CONCLUSIONS

Cardno ChemRisk performed an evaluation the skin irritation and skin sensitization potential of the WEN ingredients using the OECD profilers.

Thirty-five ingredients were run through the OECD toolbox profilers for skin irritation and skin sensitization. Five chemicals had a structural alert for skin irritation/corrosion by the inclusion rules: behentrimonium methosulfate, dicetyldimonium chloride, phenoxyethanol, tocopherol and vanillin. Four of the ingredients have experimental data (or data from a similar chemical) on skin irritation. Dicetyldimonium chloride had no *in vivo* data. All five of the ingredients are used in personal care products. Eight chemicals had structural alerts for skin sensitization including methylchloroisothiazolinone, methylisothiazolinone, panethol, stearmidopropyl dimethylamine, pelargonium graveolens oil, PCA/Sodium PCA, and hydrolyzed rice protein. Four of the ingredients had experimental skin sensitization data. Pelargonium graveolens oil, PCA/Sodium PCA, and hydrolyzed rice protein did not have skin sensitization data. All eight ingredients are commonly used in personal care products. Ingredients that had a structural alert but no experimental data may be considered for further *in silico* (e.g., QSAR) or experimental analysis to determine if their potential for skin irritation and sensitization.

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Table 1: Results of Skin Irritation and Skin Sensitization Profilers in the OECD Toolbox for WEN Ingredients.

Cas No.	Constituent	Skin irritation/corrosion Exclusion rules byBfR	Skin irritation/corrosion Inclusion rules by BfR	Protein Binding alerts for skin sensitization	Protein binding by Oasis v1.4	Protein binding by OECD	Protein binding potency	Protein binding potency Cys (DPRA 13%)	Protein binding potency Lys (DPRA 13%)
[redacted]	Alanine (L-Alanine)	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Arginine (L-Arginine)	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Aspartic Acid (L-Aspartic Acid)	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Behentrimonium methosulfate	(Undefined) Group All Lipid Solubility <0.01g/kg	Esters of organic sulfonic or sulfuric esters	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Cetyl Alcohol	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Citric Acid	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to	DPRA less than 9%	DPRA less than 9%

[redacted]

							these reules (GSH)		
[redacted]	Dicetyldimonium Chloride	(Undefined) Group All Lipid Solubility <0.01g/kg	Quarternary organic ammonium compounds	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Ethylhexylglyceri n	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Eugenia Caryophyllus (Clove) Leaf Oil	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Glycerin	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Glycine	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Glycogen	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Histidine (L-Histidine)	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%

[redacted]

[redacted]	Hydrolyzed Rice Protein	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	Schiff base formation	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Isoleucine (L-Isoleucine)	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Menthol	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Methylchloroisothiazolinone	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	SN2	SN2	SN2	Moderately reacitve (GSH)	DPRA above 21%	DPRA above 21%
[redacted]	Methylisothiazolinone	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	SN2	SN2	SN2	Moderately reacitve (GSH)	DPRA above 21%	DPRA less than 9%
[redacted]	Panthenol (Pro-Vitamin B5)	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	Acylation	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	PCA	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	Acylation	Acylation	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Pelargonium Graveolens (Geranium) Oil	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	Michael Addition	Michael Addition	Michael Addition	Slightly reactive (GSH)	Out of mechanistic domain	Out of mechanistic domain

[redacted]

[redacted]	Phenoxyethanol	(Undefined) Group All Lipid Solubility <0.01g/kg	Ethylenglycolethers	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Phenylalanine (L-Phenylaline)	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Polysorbate-20	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Proline (L-Proline)	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Serine (L-Serine)	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Sodium Lactate	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Sodium PCA	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	Acylation	Acylation	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Stearamidopropyl Dimethylamine	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	Acylation	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%

[redacted]

[redacted]	Tetrasodium EDTA	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Threonine (L-Threonine)	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Tocopherol	(Undefined) Group All Lipid Solubility <0.01g/kg	Phenols	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Triticum Vulgare (Wheat) Starch	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Valine (L-Valine)	(Undefined) Group All Lipid Solubility <0.01g/kg	Inclusion rules not met	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%
[redacted]	Vanillin	(Undefined) Group All Lipid Solubility <0.01g/kg	Aldehydes	No alert found	No alert found	No alert found	Not possible to classify according to these reules (GSH)	DPRA less than 9%	DPRA less than 9%

[redacted]