Post Meeting Announcement

Expert Panel for Cosmetic Ingredient Safety 156th Meeting (December 7-8, 2020) - Findings

December 11, 2020

• Final Safety Assessments

- Wheat Ingredients 27 ingredients Split conclusion (safe; insufficient for 6 ingredients)
- Polysilicone-11 1 ingredient Safe
- Glycerin Ethoxylates 8 ingredients Safe with qualifications

• Tentative Safety Assessments

- Amino Acid Diacetates 2 ingredients Split (1 safe; 1 insufficient)
- Acetyl Hexapeptide-8 Amide 1 ingredient Safe ≤ 0.005%
- Basic Brown 17 1 ingredient Safe as a hair dye
- Methicones 30 ingredients Split (safe with qualifications; insufficient for airbrush use)
- Papaya 5 ingredients Insufficient Data
- Polyquaternium-6 1 ingredient Safe
- Tris(Tetramethylhydroxypiperidinol) Citrate and Hydroxy Tetramethylpiperidine Oxide 2 ingredients Safe

• Insufficient Data Announcements

- Barley Ingredients 16 ingredients
- Equisetum arvense Ingredients 5 ingredients
- Melaleuca alternifolia (Tea Tree) Ingredients 8 ingredients
- Portulaca oleracea Ingredients 4 ingredients
- Saccharum officinarum (Sugarcane) Ingredients 4 ingredients

• 156th Meeting Notes

- Director's Report
- Scientific Literature Reviews available or under development
- Next Expert Panel Meeting Thursday and Friday, March 11-12, 2021

Final Safety Assessments

Final safety assessments will be posted on the CIR website at www.cir-safety.org. Unpublished data cited as references in CIR safety assessments are available for review. Any interested person who has sound scientific evidence that a final safety assessment is incorrect may petition the Expert Panel for Cosmetic Ingredient Safety (Panel) to amend the safety assessment.

Wheat Ingredients

The Expert Panel for Cosmetic Ingredient Safety (Panel) issued a final report with the conclusion that the following 21 wheat-derived ingredients are safe in cosmetics in the present practices of use and concentrations described in this safety assessment:

Triticum Aestivum (Wheat) Flour Lipids Triticum Vulgare (Wheat) Flour Lipids Triticum Aestivum (Wheat) Germ Extract Triticum Vulgare (Wheat) Germ Triticum Aestivum (Wheat) Seed Extract Triticum Vulgare (Wheat) Germ Extract Triticum Monococcum (Wheat) Seed Extract Triticum Vulgare (Wheat) Germ Powder* Triticum Vulgare (Wheat) Germ Protein Triticum Spelta Seed Water Triticum Turgidum Durum (Wheat) Seed Extract* Triticum Vulgare (Wheat) Gluten Triticum Vulgare/Aestivum (Wheat) Grain Extract* Triticum Vulgare (Wheat) Gluten Extract Triticum Vulgare (Wheat) Bran Triticum Vulgare (Wheat) Kernel Flour Triticum Vulgare (Wheat) Bran Extract Triticum Vulgare (Wheat) Seed Extract

Triticum Vulgare (Wheat) Bran Lipids Wheat Germ Glycerides
Triticum Vulgare (Wheat) Flour Extract

However, the Panel also concluded that the available data are insufficient to make a determination of safety on the following 6 wheat-derived ingredients:

Triticum Aestivum (Wheat) Leaf Extract**

Triticum Aestivum (Wheat) Peptide**

Triticum Monococcum (Wheat) Stem Water

Triticum Vulgare (Wheat) Sprout Extract

Triticum Vulgare (Wheat) Straw Water**

The data needed to determine the safety of these ingredients are:

- · Composition and impurities data
 - If significantly different from the ingredients considered safe: dermal irritation and sensitization data at maximum use concentration are needed

The Panel noted that it had previously concluded that Hydrolyzed Wheat Protein and Hydrolyzed Wheat Gluten were safe for use in cosmetics when formulated to restrict peptides to an average molecular weight of 3500 Da or less. This conclusion was in response to reports of type 1 (IgE-mediated) immediate hypersensitivity reactions that occurred in sensitized individuals following exposure to cosmetic products that contained one of these two ingredients with molecular weights greater than this limit. However, based on the available information, none of the wheat-derived ingredients in this report are hydrolyzed and most are not even proteins. Coupled with lack of reports to the contrary or experience with such reactions to these ingredients in the clinical setting, concern over such reactions to these ingredients was mitigated. If the protein ingredients in this report are hydrolyzed in processing, then the Panel needs to be made aware of these methods of manufacturing to further assess the safety of these ingredients.

Polysilicone-11

The Panel issued a final report with the conclusion that Polysilicone-11 is safe in the present practices of use and concentration described in the safety assessment. A supplier reported that this ingredient is the product of a pure addition reaction, forming no impurities and resulting in no residual monomers. The safety of this ingredient was supported by sufficient sensitization/irritation data, and lack of adverse clinical reports. In addition, as this ingredient is reported to have a large molecular weight, it is unlikely to penetrate the skin, mitigating the concern for systemic toxicity.

According to 2020 VCRP data, Polysilicone-11 is reported to be used in 440 formulations, 432 of which are leave-on formulations. Results of the concentration of use survey conducted by Council in 2018, and updated in 2019, indicate Polysilicone-11 is used at a maximum concentration of up to 19.9% in other skin care preparations.

Glycerin Ethoxylates

The Panel issued a final report with the conclusion that the following 8 glycerin ethoxylate ingredients are safe in the present practices of use and concentration as described in the safety assessment, when formulated to be non-irritating:

Glycereth-3 Glycereth-12 Glycereth-26
Glycereth-7 Glycereth-18 Glycereth-31
Glycereth-8 Glycereth-20

Glycereui-20

The Panel deemed the relevant safety data to be sufficient, as well as the complete experimental details received for previously-submitted HRIPT summaries, to be sufficient. Mild erythema reactions observed during induction were considered indicative of irritation potential.

^{*}Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

^{**}There are currently no uses reported for these ingredients.

Tentative Safety Assessments

For those tentative safety assessments below to be posted on the CIR website at www.cir-safety.org on or before January 8, 2021, interested persons are given 60 days from the posting date (March 8, 2021) to comment, provide information, and/or request an oral hearing before the Expert Panel for Cosmetic Ingredient Safety. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, and are available for review by any interested party. Please submit data and/or comments to CIR as soon as possible, but no later than 60 days from the actual posting date, for full consideration. Submissions received thereafter may be in jeopardy of not being considered by the Panel. The updated reports may be scheduled for review by the Expert Panel as early as at its March 11-12, 2021 meeting. However, some of the tentative safety assessments below may be posted later (with an appropriate 60-day comment period) and likely be scheduled for review by the Panel at its September 13-14, 2021 meeting.

Amino Acid Diacetates

The Panel issued a tentative report with the conclusion that Tetrasodium Glutamate Diacetate is safe in cosmetics in the present practices of use and concentration described in the safety assessment. However, the Panel concluded that the data were insufficient to make a determination of safety for Beta-Alanine Diacetic Acid. The additional data needed to determine safety for this cosmetic ingredients are:

- Method of manufacturing
- · Composition and impurities
- Concentration of use
- Dermal irritation and sensitization data at maximum expected use concentration
- 28-day dermal toxicity data
 - o If positive, developmental and reproductive toxicity and genotoxicity data may be needed

The Panel found that the systemic toxicity data, including developmental and reproductive toxicity studies, acute and subchronic toxicity studies, and dermal irritation and sensitization studies in this report were sufficient for assessing safety for reported cosmetic uses of Tetrasodium Glutamate Diacetate. The Panel noted that Tetrasodium Glutamate Diacetate is slowly absorbed through the gastrointestinal tract: dermal absorption is likely to be even slower. The Panel also noted the lack of carcinogenicity data and was concerned about the report by a supplier that Tetrasodium Glutamate Diacetate may contain a salt of nitrilotriacetic acid, a 2B carcinogen according to the International Agency for Research on Cancer; however, this concern was mitigated by the multiple genotoxicity studies that were negative, and the low use concentrations of this ingredient in leave-on products.

Acetyl Hexapeptide-8 Amide

The Panel concluded that Acetyl Hexapeptide-8 Amide is safe in cosmetics at concentrations up to 0.005%, and that the available data are insufficient for evaluating safety at higher concentrations. A revised tentative report with this conclusion was issued.

Acetyl Hexapeptide-8 Amide (CAS No. 616204-22-9) is defined as the product obtained by the acetylation of hexapeptide-8 in which the C-terminus is an amide. Initially, the title of this safety assessment was Acetyl Hexapeptide-8 and Acetyl Hexapeptide-8 Amide. However, it has since been determined that Acetyl Hexapeptide-8 Amide is synonymous with Acetyl Hexapeptide-8, acetyl hexapeptide-3, Acetyl Hexapeptide-24, and Acetyl Hexapeptide-24 Amide. The sequence for this acetylated and amidated peptide is Ac-Glu-Glu-Met-Gln-Arg-NH₂.

The Panel noted that the available *in vitro* and *in vivo* data indicate that Acetyl Hexapeptide-8 Amide may have drug activity (i.e., anti-wrinkle effect) by exerting an effect on type I and type III collagen in the dermis at a concentration of 10%. The Panel also stated their awareness of a consumer product purported to contain 10 to 30% Acetyl Hexapeptide; however, whether this product is a drug or cosmetic remains unknown. The Panel recognizes that Acetyl Hexapeptide-8 Amide is used in leave-on cosmetic products at concentrations up to 0.005%, based on vetted information sources, and that a drug effect (i.e., anti-wrinkle effect) on the dermis would not be likely at this low concentration. Nonetheless, the Panel acknowledges that the drug effect may be apparent at higher use concentrations.

The Panel noted the absence of systemic toxicity and detailed genotoxicity data on Acetyl Hexapaptide-8 Amide. Still, concern over the lack of these data was mitigated, after considering the peptide structure of this ingredient, the associated low partitioning coefficient of -6.3 (percutaneous absorption unlikely), and the low maximum use concentration of 0.005% in leave-on cosmetic products. On the subject of potential percutaneous absorption, the Panel also noted differing degrees of reported skin penetration by Acetyl Hexapeptide-8 Amide with *in vitro* models. The Panel felt that studies that utilized liquid chromatography with tandem mass spectrometry to measure the peptide were most dependable, and noted that these studies indicated minimal skin penetration.

Finally, the Panel agreed that a no-observed-adverse-effect-level (NOAEL) for type I and type III collagen synthesis would be needed in order to evaluate the safety of Acetyl Hexapeptide Amide in cosmetic products at concentrations > 0.005%.

Basic Brown 17

The Panel issued a tentative report with the conclusion that Basic Brown 17 is safe for use in hair dye products; however, the data are insufficient to make a determination of safety for use in other cosmetic product types.

The additional data needed for use in other cosmetic product types are:

- Concentration of use and reported function for the non-hair coloring product uses that were reported in the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database
- Dermal irritation and sensitization data at maximum use concentrations

Basic Brown 17 is reported to function as a direct, non-oxidative hair dye in hair coloring products. The Panel recognizes that hair dyes containing this ingredient, as coal tar hair dye products, are exempt from certain adulteration and color additive provisions of the Federal Food, Drug, and Cosmetic Act, when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Panel expects that following this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures. The Panel considered concerns that such self-testing might induce sensitization, but agreed that there was not a sufficient basis for changing this advice to consumers at this time.

The Panel expressed concern over the mixed results in the genotoxicity studies and the lack of carcinogenicity studies. However, the Panel noted that the toxicokinetic studies show that Basic Brown 17 does not absorb through the skin and that a conservative margin of safety calculation yielded a result of 1000. These findings, coupled with the short exposure time as a rinse-off product, helped mitigate these concerns.

Methicones

The Panel issued a revised tentative amended report, with a split conclusion, for these 30 ingredients. Specifically, the Panel concluded that these ingredients are safe as used in the present practices of use and concentration as described in this report, when formulated to be non-irritating; however, the Panel also concluded that the data are insufficient to support the safety of products containing these ingredients when applied via airbrush technology.

C26-28 Alkyl Methicone* Amino Bispropyl Dimethicone Dimethoxysilyl Ethylenediaminopropyl Dimethicone Aminopropyl Dimethicone C30-45 Alkyl Dimethicone Hexyl Dimethicone Amodimethicone C30-45 Alkyl Methicone Hexyl Methicone* Amodimethicone Hydroxystearate* Hydroxypropyldimethicone* C30-60 Alkyl Dimethicone Behenoxy Dimethicone C32 Alkyl Dimethicone* Methicone C20-24 Alkyl Dimethicone Stearamidopropyl Dimethicone* Caprvl Dimethicone Caprylyl Methicone Stearoxy Dimethicone C20-24 Alkyl Methicone* C24-28 Alkyl Dimethicone* Cetearyl Methicone Stearyl Dimethicone C24-28 Alkyl Methicone Cetyl Dimethicone Stearyl Methicone C26-28 Alkyl Dimethicone Dimethicone Vinyl Dimethicone

The Panel was made aware at this meeting that Dimethicone and Methicone are used in consumer products which are applied via aerosolized airbrush devices. The Panel considered information suggesting that airborne particles resulting from airbrush delivery are respirable, and, consequently, that more information on particle size distribution and the present concentrations of use for these ingredients in airbrush products is needed. Additionally, the Panel discussed how the types of airbrush products these ingredients are used in would affect the exposure duration and frequency (e.g., daily, brief foundation application, compared to periodic, but longer suntan spray exposure). Thus, the Panel reasoned that these additional data, including more inhalation toxicity data for respirable particles, were warranted to make a determination of safety for this product category.

Papaya Ingredients

The Panel issued a tentative report for public comment with the conclusion that the available data are insufficient to make a determination that the following 5 *Carica papaya*-derived ingredients are safe under the intended conditions of use in cosmetic formulations:

Carica Papaya (Papaya) Fruit Carica Papaya (Papaya) Fruit Juice Carica Papaya (Papaya) Leaf Extract Carica Papaya (Papaya) Fruit Water*

In order to determine safety for Carica Papaya (Papaya) Fruit, Carica Papaya (Papaya) Fruit Extract, Carica Papaya (Papaya) Fruit Juice, and Carica Papaya (Papaya) Fruit Water, the Panel has requested phototoxicity/photosensitization data. These data have been requested due to the fact that the existing studies in the report regarding phototoxicity/photosensitization on Carica Papaya (Papaya) Fruit Extract include an SPF 50 sunscreen lotion as part of the test formulation. It is unknown whether the ingredients in this sunscreen formulation would inhibit the potential phototoxicity/photosensitization of Carica Papaya (Papaya) Fruit Extract. In lieu of phototoxicity data on the papaya-derived fruit ingredients, the Panel would also accept a clarification on the specific ingredients of the SPF 50 lotion in the existing phototoxicity/photosensitization assays. In addition, in order to determine safety for Carica Papaya (Papaya) Leaf Extract, the Panel has requested genotoxicity, irritation, sensitization, and phototoxicity/photosensitization data.

Polyquaternium-6

The Panel issued a tentative report for public comment with the conclusion that Polyquaternium-6 is safe in cosmetics in the present practices of use and concentration described in the safety assessment.

The Panel noted that most of the safety test data in this report are on high molecular weight Polyquaternium-6 (42%, MW 150,000 Da, 6.5% monomer content). It was agreed that, overall, the available data are not indicative of any safety concerns relating to skin sensitization, systemic toxicity, or other toxicity endpoints, while acknowledging the polymer and monomer content of the test substance administered. The Panel considered the limited, negative skin sensitization/photosensitization data in this safety assessment, but noted that potential concerns relating to systemic exposure, in the absence of additional data, would be mitigated because this ingredient would not be percutaneously absorbed.

The Panel discussed the issue of incidental inhalation exposure from the use of Polyquaternium-6 in hair sprays (pump sprays) at maximum use concentrations up to 0.5%. The Panel stated that droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of Polyquaternium-6. Finally, the Panel cautions that products containing Polyquaternium-6 should be formulated to avoid the formation of nitrosamines.

^{*}Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

^{*}not reported to be in use

Tris(Tetramethylhydroxypiperidinol) Citrate and Hydroxy Tetramethylpiperidine Oxide

The Panel issued a tentative report concluding that these 2 ingredients are safe as used in the present practices of use and concentration in cosmetics as described in the safety assessment. The Panel determined that the low maximum reported dermal concentration and high NOAEL of 150 mg/kg bw/d Tris(Tetramethylhydroxypiperidinol) Citrate (at 97.3% purity) from a 90-d dermal toxicity study, as well as robust toxicological data for both ingredients, were sufficient to support safety.

Insufficient Data Announcements

For these insufficient data announcements, interested persons are given an opportunity to comment, provide information and/or request an oral hearing before the Panel. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, and are available for review by any interested party. Please submit data and/or comments to CIR as soon as possible, but no later than February 9, 2021, for full consideration. Submissions received thereafter might not be considered by the Panel at their next meeting. These reports may be scheduled for review by the Panel as soon as the March 11-12, 2021 meeting.

Barley Ingredients

The Panel issued an Insufficient Data Announcement (IDA) for the following 16 barley-derived ingredients:

Hordeum Distichon (Barley) Extract Hordeum Distichon (Barley) Seed Flour Hordeum Vulgare Extract Hordeum Vulgare Flower/Leaf/Stem Juice Hordeum Vulgare Juice Hordeum Vulgare Leaf Extract Hordeum Vulgare Leaf Juice Hordeum Vulgare Leaf Powder Hordeum Vulgare Leaf/Stem Powder
Hordeum Vulgare Powder
Hordeum Vulgare Root Extract
Hordeum Vulgare Seed Extract
Hordeum Vulgare Seed Flour
Hordeum Vulgare Seed Water
Hordeum Vulgare Sprout Extract
Hordeum Vulgare Stem Water

The additional data needed to determine safety for these cosmetic ingredients are:

- 28-day dermal toxicity data on the whole plant extracts Hordeum Distiction (Barley) Extract and Hordeum Vulgare Extract
 - o If positive, developmental and reproductive toxicity and genotoxicity data may be needed
 - o Alternatively, acceptable evidence of safe use as a food for ingredients derived from the flower, leaf, stem, and root
- Dermal irritation and sensitization data at maximum concentration of use for the whole plant extracts Hordeum Distichon (Barley) Extract and Hordeum Vulgare Extract

Equisetum arvense Ingredients

The Panel issued an IDA with the following data requests on the Equisetum arvense-derived ingredients that are listed below:

Equisetum Arvense Juice, Equisetum Arvense Leaf Extract, Equisetum Arvense Leaf Powder, and Equisetum Arvense Powder

Method of manufacture, impurities, and composition data

Equisetum Arvense Extract

• Skin irritation and sensitization data at maximum concentration of use

The Panel also noted that hair loss was observed in an oral dosing study in which Sprague-Dawley rats were fed 4% Equisetum arvense powder in a cholesterol diet for 14-d. However, they also noted no obvious clinical signs in another study in which F344 rats were fed *Equisetum arvense* (hot water extract of powder) at concentrations up to 3% in a basal diet for 13 wk.

Melaleuca alternifolia (Tea Tree) Ingredients

The Panel reviewed the assessment of 8 Melaleuca alternifolia (tea tree)-derived ingredients as used in cosmetics for the first time, and found the data were insufficient to determine safety of these ingredients.

Melaleuca Alternifolia (Tea Tree) Extract
Melaleuca Alternifolia (Tea Tree) Leaf Extract
Melaleuca Alternifolia (Tea Tree) Flower/Leaf/Stem Extract
Melaleuca Alternifolia (Tea Tree) Leaf Oil
Melaleuca Alternifolia (Tea Tree) Leaf Powder
Melaleuca Alternifolia (Tea Tree) Leaf
Melaleuca Alternifolia (Tea Tree) Leaf Water

The Panel noted that the majority of the data included in the report were on tea tree oil; this name is not an International Nomenclature Cosmetic Ingredient (INCI) name. Although the report was robust with data for tea tree oil, and the Panel considered these data relevant to the oil ingredients in the report (i.e., Melaleuca Alternifolia (Tea Tree) Flower/Leaf/Stem Oil and Melaleuca Alternifolia (Tea Tree) Leaf Oil), it was not clear to the Panel whether those data are also relevant to the non-oil ingredients. Accordingly, the Panel issued an IDA requesting the following:

- Methods of manufacture, composition, and impurities data for the non-oil ingredients named above
 - o if these are significantly different from data on the oils, then irritation and sensitization data for Melaleuca Alternifolia (Tea Tree) Extract at the expected maximum concentration of use, and other toxicity endpoints, specifically to include genotoxicity data, may be needed

Portulaca oleracea Ingredients

The Panel issued an IDA for these 4 Portulaca oleracea-derived ingredients:

Portulaca Oleracea Extract
Portulaca Oleracea Flower/Leaf/Stem Extract

Portulaca Oleracea Juice Portulaca Oleracea Water

The data needed to determine safety include:

- Clarification on the current maximum concentration of use
- A 28-d dermal toxicity study at the maximum concentration of use (preferably with the ingredient in an hydroalcoholic solvent)
 - o If these data are positive, further systemic toxicity data may be needed
- An Ames test (preferably with the ingredient in an hydroalcoholic solvent)

Saccharum officinarum (Sugarcane) Ingredients

The Panel issued an IDA for the following 4 Saccharum officinarum (sugarcane)-derived ingredients:

Saccharum Officinarum (Sugarcane) Bagasse Powder Saccharum Officinarum (Sugarcane) Extract Saccharum Officinarum (Sugarcane) Juice Extract Saccharum Officinarum (Sugarcane) Wax

In order to arrive at a conclusion of safety for this ingredient group, the Panel requested:

• Sensitization/irritation data for Saccharum Officinarum (Sugarcane) Extract at the maximum concentration of use

156th Meeting Notes

Director's Report

Dr. Heldreth expressed gratitude for the Panel's and other stakeholders' continued support of the Cosmetic Ingredient Review program. He also noted that 2020 has been a remarkably interesting year for all, CIR included. For the first time, the meetings of the Expert Panel were 100% virtual and the Panel also got a new team leader. Dr. Heldreth again welcomed Dr. Cohen, who stepped into the team leader role at this meeting. The consensus was that he had done a marvelous job.

Dr. Heldreth mentioned that he has always enjoyed learning. Since he joined CIR in 2010, he felt like he has learned so much from the experts at the table. He felt extremely fortunate to have such wonderful teachers, and, he was not the only one who felt this way. Indeed, in 2020, Dr. Bergfeld was awarded the Cleveland Clinic Foundation Dermatology Teacher of the Year Award, the American Academy of Dermatology's Thomas Pearson Memorial Education Award, and the Accreditation Council for Graduate Medical Education's Parker J. Palmer Courage to Teach Award. Dr. Heldreth concluded by reiterating his gratitude to each and every person present for making this Panel what it is.

Scientific Literature Reviews

The following Scientific Literature Reviews are posted at the CIR website or are currently under development and may be posted imminently. These may then be presented to the Panel for their review (as Draft Reports) during the next few meetings.

- Acrylate/Acrylamide Copolymers
- Acryloyloxyethyl Phosphorylcholine Polymers
- Diatomaceous Earth
- Fatty Esters End-Capped Alkoxylates
- Fatty Ethers
- Glucosamines

- Glyceryl Acrylates
- Glycolactones
- Hydroxyacetophenone
- Olea europaea-Derived Ingredients
- Rosa damascena-derived Ingredients
- Salvia officinalis-Derived Ingredients

Next CIR Expert Panel Meeting

Thursday and Friday, March 11-12, 2021, to be held virtually via Microsoft Teams.

Please submit a request for an invitation prior to the meeting if you would like to attend. The link will be available approximately a month before the meeting and will be found on the 157th meeting page of the CIR website. https://www.cir-safety.org/