Safety Assessment of Wheat-Derived Ingredients as Used in Cosmetics

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All interested persons are provided 60 days from the above release date (August 18, 2019) to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. 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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer.

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INTRODUCTION

Most of wheat-derived ingredients detailed in this safety assessment are reported to function in cosmetics as skin conditioning agents, while some are reported to have other functions, such as abrasives, absorbents, antioxidants, bulking agents, film formers, flavoring agent, hair conditioning agents, and viscosity increasing agents, according to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*; see Table 1).[1] Functions such as skin bleaching agent (for Triticum Vulgare (Wheat) Germ Extract) are not considered cosmetic functions in the United States (US) and, therefore, do not fall under the purview of the Cosmetic Ingredient Review (CIR). This assessment of the safety of the following 24 wheat-derived ingredients is based on the data contained in this report:

Triticum Aestivum (Wheat) Flour Lipids
Triticum Aestivum (Wheat) Germ Extract
Triticum Aestivum (Wheat) Leaf Extract
Triticum Aestivum (Wheat) Peptide
Triticum Aestivum (Wheat) Seed Extract
Triticum Monococcum (Wheat) Seed Extract
Triticum Monococcum (Wheat) Stem Water
Triticum Spelta Seed Water
Triticum Turgidum Durum (Wheat) Seed Extract
Triticum Vulgare/Aestivum (Wheat) Grain Extract
Triticum Vulgare (Wheat) Bran
Triticum Vulgare (Wheat) Bran Extract
Triticum Vulgare (Wheat) Bran Lipids
Triticum Vulgare (Wheat) Flour Extract
Triticum Vulgare (Wheat) Flour Lipids
Triticum Vulgare (Wheat) Germ
Triticum Vulgare (Wheat) Germ Extract
Triticum Vulgare (Wheat) Germ Powder
Triticum Vulgare (Wheat) Germ Protein
Triticum Vulgare (Wheat) Kernel Flour
Triticum Vulgare (Wheat) Protein
Triticum Vulgare (Wheat) Seed Extract
Triticum Vulgare (Wheat) Sprout Extract
Triticum Vulgare (Wheat) Straw Water

The safety of Triticum Vulgare (Wheat) Kernel Flour was previously reviewed by the CIR Expert Panel (Panel) and the conclusion of "safe … in the present practices of use and concentration" was published in 1980 and reaffirmed in a re-review that was published in 2003.[2,3] Because it has been more than 15 years since the safety of Triticum Vulgare (Wheat) Kernel Flour was reviewed, it is included in this safety assessment for re-review.

The Panel has reviewed the safety of several additional wheat-derived ingredients including Wheat Amino Acids[4], Triticum Vulgare (Wheat) Starch[2,3,5], Hydrolyzed Triticum Spelta Starch[5], Hydrolyzed Wheat Starch[5], Triticum Vulgare (Wheat) Gluten,[2,6] Wheat Germ Glycerides,[2,6] Triticum Aestivum (Wheat) Germ Oil,[7] Triticum Vulgare (Wheat) Germ Oil,[2,7,8] Triticum Vulgare (Wheat) Germ Oil Unsaponifiables,[7] Hydrogenated Wheat Germ Oil[7], and Hydrogenated Wheat Germ Oil Unsaponifiables.[7]. The Panel concluded that all of these ingredients are safe in the present practices of use and concentration in cosmetics. The Panel also reviewed Hydrolyzed Wheat Protein and Hydrolyzed Wheat Gluten and concluded that these ingredients are safe for use in cosmetics when formulated to restrict peptides to an average molecular weight of 3500 Daltons or less.[9] This conclusion is in response to reports of types 1 immediate hypersensitivity reactions that occurred in sensitized individuals following exposure to cosmetic products that contained these two ingredients with molecular weights greater than this limit. Polypeptides must be at least 30 amino acids long (i.e. molecular weights of about 3570 Daltons to interact with the two IgE-binding epitopes) to elicit type 1 hypersensitivity reactions.

Most of the ingredients reviewed in this safety assessment may be consumed as food, and daily exposure from food use would result in much larger systemic exposures than those from use in cosmetic products. The primary focus of the safety assessment of these ingredients as used in cosmetics is on the potential for effects from topical exposure. Proteins from wheat in the diet, specifically wheat gluten, are associated with adverse health conditions (such as celiac disease and dermatitis herpetiformis) in a small portion of the general population. Since the concentration of gluten in cosmetics is low, there is no likelihood that enough gluten could be absorbed by the percutaneous route or by inadvertent ingestion from cosmetic products to precipitate a flare-up of either gastrointestinal or cutaneous symptoms.[6]

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Note: In many of the published studies, it is not known how the substance being tested compares to the cosmetic ingredient. Therefore, if it is not known whether the substance being discussed is a cosmetic ingredient, the test substance will be identified as "wheat…" (e.g., wheat germ extract or wheat flour); if it is known that the substance is a cosmetic ingredient, the *Dictionary* nomenclature "Triticum Aestivum…" or "Triticum Vulgare…" (e.g., Triticum Aestivum (Wheat) Germ Extract or Triticum Vulgare (Wheat) Kernel Flour) will be used.

CHEMISTRY

Definition and Plant Identification

The definitions of the ingredients included in this review are provided in Table 1.[1] *Triticum* wheat species have been used as food staples for 10,000 years and originated in the Middle East.[10] *Triticum aestivum* L. is the most cultivated cereal grain in the world, making up about a third of total cereal grains. [11] *Triticum monococcum* is also known as eikorn and is native to eastern Europe and western Asia.[10] *Triticum turgidum* var. durum is also known as durum wheat, hard wheat, or macaroni or pasta wheat, and is commonly cultivated in the Mediterranean region.[10,12] *Triticum spelta* is considered to be an ancient wheat grain that was once prominently grown in ancient Egypt and Italy and is now grown in northern and eastern European countries.[10,13]

Table 2 lists the generic definitions of the parts of plants that are most pertinent to the ingredients in this report.[1] The wheat plant is comprised of a root and shoot system.[14] There are two types of roots: the seminal roots and the nodal roots (crown or adventitious roots). The shoot is made up of a series of repeating units or phytomers, each potentially having a node, a leaf, an elongated internode, and a bud in the axil of the leaf. The dry fruit of the wheat plant may be referred to as the seed, grain, or kernel. The embryo of the seed is also called the germ and is comprised of the scutellum, the plumule (shoot), and the radicle (primary root). The scutellum secretes some of the enzymes involved in germination and absorbs the soluble sugars that are breakdown products of the starch in the endosperm. The endosperm is surrounded by the metabolically active cell layer called the aleurone layer, the testa (seed coat), and the pericarp (fruit coat).

Triticum Vulgare (Wheat) Germ

Wheat germ is comprised of the embryonic axis and the scutellum of wheat seed and represents about 2.5% - 3.8% of total seed weight.[15] It is a by-product of the flour milling industry.

Physical and Chemical Properties

Triticum Aestivum (Wheat) Leaf Extract

The pH of wheatgrass (the young leaves of wheat) is reported to be 7.4.[16]

Triticum Vulgare (Wheat) Kernel Flour

The pH of refined wheat flours is approximately 6.0 - 6.1, while the pH of whole wheat flour is approximately 6.2.[11]

Method of Manufacture

Triticum Vulgare (Wheat) Kernel Flour

Wheat flour is produced by different forms of milling or grinding, of the grain's endosperm.[11,17] The different forms of compression and shear allow for producing different grain sizes for different end uses or flour types.

Triticum Vulgare (Wheat) Germ

Wheat germ is a by-product of flour milling and is produced by mechanical separation of the germ from whole wheat.[15]

Composition/Impurities

Yields of constituents in wheat have been found to be dependent on extraction methods and growing conditions such as soil composition, climate, duration of growth period, and height at harvest.[16] Additionally, different plant parts have different constituent compositions.

Triticum Aestivum (Wheat) Leaf Extract

At least 41 flavonoid derivatives have been identified in wheat leaf extract (extracted with 80% methanol) using liquid chromatography/mass spectrometry (LC/MS).[18] The flavone structures identified were luteolin, tricetin, apigenin, chrysoeriol, and tricin.

Wheatgrass is reported to contain chlorophyll, flavonoids, several varieties of vitamins including vitamins C and E, choline, minerals, enzymes, indoles, and a number of amino acids.[16]

Triticum Vulgare/Aestivum (Wheat) Grain Extract

Total phenolic content of wheat grain extract (as 80% methanol extracts) was 5.1 - 6.8 µg (±)-catechin/mg for endosperm and embryo and 16.0 - 16.7 µg (±)-catechin/mg for "pericarb" (pericarp) and "testa" (seedcoat).[19]

Triticum aestivum grain may be contaminated with mycotoxins such as trichothecenes and zearaleonones from toxin-producing fungi and molds.[13]

Triticum Vulgare (Wheat) Flour Extract

The yield of non-starch lipids, neutral lipids, glycolipids, and phospholipids of wheat flour extract was dependent on the solvent system used.[20] Total lipids ranged from 6.30 - 9.76 g fatty acid/kg flour, neutral lipids ranged from 3.76 - 5.43 g fatty acid/kg flour, glycolipids ranged from 1.09 - 2.98 g fatty acid/kg flour, and phospholipids ranged from 0.78 - 1.85 g fatty acid/kg flour. The five major fatty acids present in the lipid classes extracted from wheat flour were palmitic acid, stearic acid, oleic acid, linoleic acid, and linolenic acid.

Triticum Vulgare (Wheat) Germ

Wheat germ contains about 10% - 15% lipids, 26% - 35% protein, 17% sugar, 1.5% - 4.5% fiber, and about 4% minerals.[15] Bioactive constituents include tocopherols (300 - 740 mg/kg dry matter), phytosterols (24 - 50 mg/kg), policosanols (10 mg/kg), carotenoids (4 - 38 mg/kg), thiamin (15 - 23 mg/kg), and riboflavin (6 - 10 mg/kg).

There are four classes of protein in wheat flour: globulins, albumins, gliadins, and glutenins.[17] Gliadins and glutenins are components of gluten.

Triticum Vulgare (Wheat) Kernel Flour

Refined wheat flours may contain approximately 13 g/100 g dry weight protein, 0.8 - 0.9 g/100 g dry weight lipids, 85 g/100 g dry weight carbohydrates, and 9.5 g/100 g dry weight gluten.[11] Whole wheat flour contains approximately 15 g/100 g dry weight protein, 1.5 g/100 g dry weight lipids, 82 g/100 g dry weight carbohydrates, and 7 g/100 g dry weight gluten. Wheat flour may be contaminated with foodborne bacteria and fungi, including *Salmonella* spp., *Escherichia coli*, and *Bacillus cereus*. Wheat flour may also be contaminated with mycotoxins such as aflatoxins and ochratoxin A.

Triticum Vulgare (Wheat) Protein

Wheat proteins are classified into gluten and non-gluten proteins.[21] The gluten proteins are comprised of gliadins and high and low molecular weight glutenins. The non-gluten proteins are comprised of albumins and globulins.

Triticum Vulgare (Wheat) Sprout Extract

A hydroalcoholic extract of wheat sprouts was determined to be composed of hydrophilic compounds, such as peptides, and hydrophobic compounds, such as polyphenols.[22] Further extraction with 90% acetone resulted in the precipitation of 70% glutathione. Phospholipid classes identified from hydroalcoholic extract of wheat sprouts included phosphatidylethanol-amine, phosphatidylcholine, phosphatidic acid, phosphatidylinositol, and lysophosphatidylcholine.[23] These phospholipids were characterized by a high content of essential fatty acids (α-linoleic acid and α-linolenic acid).

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to the 2019 VCRP survey data, Triticum Aestivum (Wheat) Germ Extract has the most reported uses in cosmetic products with a total of 284 formulations; the majority of the uses are in leave-on skin care products (Table 3).[24] Triticum Aestivum (Wheat) Seed Extract has the second greatest reported number of uses in this safety assessment with 160 formulations; the majority of the uses are also in leave-on skin care products. All other in-use ingredients are reported to be used in significantly fewer formulations. The results of the concentration of use survey conducted by the Council in 2017 indicate that Triticum Vulgare (Wheat) Germ Extract has the highest concentration of use in a leave-on formulation; it is used at up to 13% in face powders.[25] The maximum concentrations of use for the remaining ingredients are much lower, with the next highest concentration of use reported for products resulting in leave-on dermal exposure is 0.6% in Triticum Aestivum (Wheat) Germ Extract in "other" skin care preparations. The ingredients not in use according to the VCRP and industry survey are listed in Table 4.

Triticum Vulgare (Wheat) Kernel Flour has 4 reported uses, according to 2019 VCRP data; no uses were reported in 2001.[2] The concentration of use in 2001 was reported as a range > 0.1% to 1%; a concentration of use survey has not yet been conducted by Council for this safety assessment.

Wheat-derived ingredients may be used in products that can be incidentally ingested or come into contact with the eyes or mucous membranes; for example, Triticum Vulgare (Wheat) Germ Extract is reported to be used in lipstick at up to 0.13%, Triticum Vulgare (Wheat) Protein is reported to be used in eye lotion at up to 0.16%, and Triticum Vulgare (Wheat) Bran is reported to be used in "other" personal cleanliness products at up to 0.61%.[25]

Additionally, some of the ingredients are used in cosmetic sprays and could possibly be inhaled; for example, Triticum Vulgare (Wheat) Germ Extract is reported to be used at up to 0.32% in hair spray and up to 0.11% in spray deodorant.[25] In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.[26,27] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[28,29] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[28] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. Triticum Vulgare (Wheat) Germ Extract is reportedly used in face powders at concentrations up to 13% and could possibly be inhaled.[25] Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[30-32]

The wheat-derived ingredients described in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[33]

Non-Cosmetic

The FDA requires allergen labeling when major allergens, such as wheat, are included in food.[34] A major food allergen is an ingredient from a food or food group, such as wheat, that contains protein derived from the food.

Triticum vulgare is reported to be used extensively in traditional medicine to treat decubitus ulcers, burns, scarring delays, dystrophic diseases, and to accelerate tissue repair.[35] It has been investigated for anti-inflammatory properties.

Wheat bran is an over-the-counter (OTC) laxative drug product.[36] Wheat germ is an OTC weight control drug product (21CFR§310.545).

Wheat leaf extract has been studied for therapeutic benefits for chronic fatigue syndrome, and for its immunological, anti-oxidative, and anti-cancer activities.[16,37] Wheat sprout extract has been studied for its antioxidant content and potential use as a food ingredient and in cancer treatments.[22,23,38] Wheat germ is used as a food supplement and an ingredient in several food products,[15] and wheat germ extract has also been studied for use in cancer prevention and treatment.[39]

TOXICOKINETIC STUDIES

No relevant toxicokinetics studies on wheat-derived ingredients were found in the public literature, and unpublished data were not submitted. In general, toxicokinetics data are not expected to be found on botanical ingredients because each botanical ingredient is a complex mixture of constituents.

TOXICOLOGICAL STUDIES

Most of the wheat-derived ingredients that are addressed in this safety assessment are found in the foods we consume daily. The potential for systemic effects, other than sensitization, from the possible absorption of these ingredients through the skin is much less than the potential for systemic effects from absorption through oral exposures. This is because the rates of absorption and metabolism of these ingredients in the skin are expected to be negligible compared to the corresponding rates in the digestive tract. Thus, the potential for systemic effects, other than sensitization, is not discussed in detail in this report.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Oral

Triticum Vulgare (Wheat) Sprout Extract

The effects of the water extract of wheat sprouts on spermatozoa was investigated using male BALB/c mice.[40] The mice were treated with benzo[α]pyrene (B[α]P) in corn oil (100 mg/kg bw) for 5 consecutive days via intraperitoneal injections. A control group of 19 mice only received corn oil and another 3 mice only received wheat sprout extract. Nineteen animals received the wheat sprout extract in parallel with the B[α]P treatment (3 mice received 40 ml, 10 mice received 70 ml, and 6 mice received 140 ml, in 18 equal doses by gavage) starting 3 days before the B[α]P treatment. Twenty-eight mice received just B[α]P. The sperm of the treated mice were examined 5 weeks after the B[α]P treatment. The mice treated only with B[α]P had an incidence of 61.1% for abnormally-shaped sperm heads. The corn oil control group only had sperm abnormalities observed in 1.93%. The wheat sprout extract alone did not enhance the level of sperm abnormalities in comparison with the corn oil controls. The simultaneous treatment of B(α)P and wheat sprout extract resulted in a decrease in the percentage of abnormally-shaped sperm heads when compared to the group that received just B[α]P, but not in a dose-dependent manner.

GENOTOXICITY

In Vitro

Triticum Vulgare (Wheat) Bran Extract

The genotoxicity potential of a wheat bran extract that was highly-enriched in arabinoxylan-oligosaccharides was assessed in an Ames test using *S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 and *E. coli* strain WP2uvrA, with and without metabolic activation.[41] The extract was dissolved at 100 mg/ml in distilled water and was tested at 5, 15.8, 50, 158, 500, 1581, and 5000 µg/plate. Strain-specific positive and negative control chemicals were used and yielded expected results. Wheat bran extract was not mutagenic at up to 5000 µg/plate.

The same researchers assessed the clastogenic potential of the same wheat bran extract in a chromosome aberration assay using Chinese hamster lung fibroblast V79 cells.[41] The cells were treated for 3 h or 20 h with the extract at up to 5000 µg/ml, with and without metabolic activation. No biologically significant increases in the number of cells showing structural chromosome aberrations were observed. The wheat bran extract was not clastogenic in this assay.

ANTI-MUTAGENICITY

In Vitro

Triticum Vulgare (Wheat) Sprout Extract

The ability of the S-30 fraction of the water extract of wheat sprouts to inhibit mutagenicity was assessed in an Ames test using *S. typhimurium* strain TA 98, with metabolic activation and in the presence of 7,12-dimethyl benz[a]anthracene (DMBA) (50 µg/plate).[40] A decrease in the number of revertants was observed. No further details were provided.

In Vivo

Triticum Vulgare (Wheat) Sprout Extract

The same research group from the above study investigated the effects of the S-30 fraction of the wheat sprout extract on the ability of BALB/c mouse skin enzymes to activate DMBA to mutagenic metabolites.[40] The S-9 fraction from the mouse skin that received the wheat extract subcutaneously for 4 days (0.1 ml/day) still activated DMBA (single painting; 100 µg/mouse) to mutagenic metabolites for the *S. typhimurium* strain TA 98, but the ability was 20% lower than that of the S-9 fraction from mice that did not receive the wheat sprout extract. No further details were provided.

CARCINOGENICITY

Co-Carcinogenicity

Triticum Vulgare (Wheat) Bran

In a 31-week dietary study, a group of 12 male Sprague-Dawley rats received 20% wheat bran as a dietary supplement during and after administration of 1,2-dimethylhydrazine (a carcinogen) via 13 weekly subcutaneous injections.[42] Another group of 12 rats was fed the wheat bran in conjunction with administration of the carcinogen, and then switched to the control diet after 13 weeks. A third group of 11 rats received a fiber-free (control) diet during the administration of the carcinogen, and then switched to the wheat bran diet after 13 weeks. The control group (12 rats) received a fiber-free diet throughout the 31 weeks. In both groups that received wheat bran in conjunction with administration of the carcinogen, small intestinal or colonic tumor yield was significantly greater, with benign and malignant tumors incidences increased by 3.4-fold ($p < 0.005$), adenoma incidences increased by 3.5-fold ($p < 0.025$), and adenocarcinomas incidences increased by 3.25-fold ($p < 0.05$) when compared to rats that received a control diet. Rats that received wheat bran only after carcinogen exposure had a reduced number of benign adenomas (71.4%; $p < 0.025$) when compared to the rats that received control diet. The rats fed the wheat bran during carcinogen administration and then switched to the control diet had the highest tumor yield, with 4.5 times as many benign and malignant tumors as the control rats ($p < 0.05$), and at least 6 times as many adenomas as any of the other dietary groups ($p < 0.05$).

Tumor Promotion

Triticum Vulgare (Wheat) Sprout Extract

The tumorigenic effects of wheat sprout extract (S-30 fraction) were investigated using 8-week-old male BALB/c mice.[40] Skin papillomas were initiated by painting the skin of mice with an acetone solution of DMBA (100 µg/mouse). Twice weekly treatments of croton oil dissolved in acetone (10 µl) was used for papilloma growth promotion. The mice received the promoter for 22 weeks. One group of mice (n = 38) received 10 successive subcutaneous injections of wheat sprout extract (0.1 ml) starting on day 3 before DMBA treatment) with the croton oil promoter, while another group (n = 8) received the extract during the promotion period without the croton oil promoter. Further groupings involved giving mice the wheat sprout extract (0.1 ml) subcutaneously twice a week for 22 weeks without the croton oil promoter during both the initiator and promoter phases (n = 13). Wheat sprout extract, when injected subcutaneously for 10 days during carcinogenesis initiation in mice, shortened the latency period from 9 to 4 weeks and increased the number of skin papillomas by 4-fold.

When the extract was applied to mice treated with DMBA, but did not have croton oil promotion, only one mouse developed papillomas during the 24 weeks. Controls where the extract was injected alone without initiation or promotion did not produce skin papillomas (n = 17). The authors concluded that wheat sprout extract did not have initiating or promoting properties.

Anti-Tumor Promotion

Triticum Aestivum (Wheat) Leaf Extract

The effects of wheatgrass extract on skin papillomagenesis induced by DMBA and croton oil were investigated in male Swiss albino mice.[43] The mice were divided into five groups of 10: Group 1 was the control group that received a single dose of DMBA (100 µl/50 µl acetone) on shaved dorsal skin followed two weeks later by croton oil (1% in 100 µl acetone) three times a week for a total of 16 weeks; Group 2 (pre-group) received wheatgrass leaf extract orally (20 ml/kg bw) for 7 days prior to the application of DMBA and croton oil in the manner that Group 1 received these; Group 3 (peri-group) was treated with DMBA and then received wheatgrass leaf extract for 15 days prior to receiving the croton oil, as in Group1; Group 4 (post-group) was treated with DMBA as in Group 1 and received wheatgrass leaf extract at the same time the croton oil treatment started; and Group 5 received the wheatgrass leaf extract seven days prior to and after the treatment with DMBA and through the treatment of croton oil until experiment end (total number of exposure days not stated). Tumor incidence, yield, and burden in Groups 2-5 were significantly decreased as compared to Group 1. The average latent period was increased in Groups 2-5, with the longest latent period being observed in Group 5.

IRRITATION AND SENSITIZATION

Human

Triticum Vulgare (Wheat) Germ Extract

A human repeated insult patch test (HRIPT) of a face and body powder containing 13% Triticum Vulgare (Wheat) Germ Extract was conducted in 105 subjects.[44] The test material (200 mg) was applied to the test sites as supplied. The patches were partially occlusive and 2 cm^2 in size. No irritation or sensitization was observed.

No other dermal sensitization studies for wheat-derived ingredients were found in the published literature, and unpublished data were not submitted.

Ocular Irritation Studies

No ocular irritation studies were found in the published literature, and unpublished data were not submitted.

OCCUPATIONAL EXPOSURES

Work-related sensitization (IgE mediated) to wheat flour and grain dusts has been reported in bakery.[45-47] Symptoms typically include rhinitis and asthma and other respiratory symptoms, but may also include contact urticaria and hand eczema. Skin-prick testing, skin biopsies, and radioallergosorbent tests (RAST) have been utilized to identify and analyze the reactions observed in bakery workers.

SUMMARY

Most of the 24 wheat-derived ingredients detailed in this safety assessment are reported to function in cosmetics as skin conditioning agents, while some are reported to have other functions, such as abrasives, absorbents, antioxidants, bulking agents, film formers, flavoring agent, hair conditioning agents and viscosity increasing agents. Functions such as skin bleaching agent (for Triticum Vulgare (Wheat) Germ Extract) are not considered cosmetic functions in the US and, therefore, do not fall under the purview of the CIR.

Yields of constituents in wheat have been found to be dependent on extraction methods and growing conditions such as soil composition, climate, duration of growth period, and height at harvest. Additionally, different plant parts have different constituent compositions. Wheat grain may be contaminated by mycotoxins, such as aflatoxins, trichothecenes, and zearalenones. Wheat flour may be contaminated with mycotoxins and foodborne bacteria and fungi, such as *Salmonella* spp., *E. coli*, and *B. cereus*.

According to the 2019 VCRP survey data, Triticum Aestivum (Wheat) Germ Extract has the most reported uses in cosmetic products with a total of 284 formulations; the majority of the uses are in leave-on skin care products. Triticum Aestivum (Wheat) Seed Extract has the second greatest reported number of uses in this safety assessment with 160 formulations; the majority of the uses are also in leave-on skin care products. All other in-use ingredients are reported to be used in significantly fewer formulations. The results of the concentration of use survey conducted by the Council indicate that Triticum Vulgare (Wheat) Germ Extract has the highest maximum concentration of use in a leave-on formulation; it is used at up to 13% in face powders. The concentrations of use for the remaining ingredients are much lower; the next highest maximum concentration of use reported for products resulting in leave-on dermal exposure is 0.6% in Triticum Aestivum (Wheat) Germ Extract in “other” skin care preparations. Triticum Vulgare (Wheat) Kernel Flour has 4 reported uses in 2019;

no uses were reported in 2001. The concentration of use in 2001 was reported as a range > 0.1% to 1%; a concentration of use survey has not yet been conducted by Council for this safety assessment.

Wheat is considered a major food allergen and is required to be labeled as such by the FDA when included in food. *Triticum vulgare* is reported to be used extensively in traditional medicine and it has been investigated for anti-inflammatory properties. Wheat bran is an OTC laxative drug product, and wheat germ is an OTC weight control drug product. Wheat leaf extract and wheat germ extract have been studied for various therapeutic effects and for use in food supplements.

Most of the wheat-derived ingredients that are addressed in this safety assessment are found in the foods we consume daily. The potential for systemic effects, other than sensitization, from the possible absorption of these ingredient through the skin is much less than the potential for systemic effects from absorption through oral exposures. This is because the rates of absorption and metabolism of these ingredients in the skin are expected to be negligible compared to the corresponding rates in the digestive tract.

Sperm abnormalities were not observed in mice that received wheat sprout extract (40 - 140 ml) orally, and sperm abnormalities were decreased in mice that received the extract with simultaneous treatment of B[α]P.

Wheat bran extract was not mutagenic in an Ames test at up to 5000 µg/plate, nor was it clastogenic in Chinese hamster lung fibroblasts in a chromosome aberration assay at up to 5000 µg/ml. In anti-mutagenicity studies, a decrease in the number of revertants was observed following exposure to the S-30 fraction of a water extract of wheat sprouts in an Ames test with metabolic activation and DMBA. A decrease in mutagenic metabolites was observed in BALB/c mouse skin following subcutaneous exposure to the same wheat sprout extract (0.1 ml/day) and DMBA.

Tumor incidences were increased in a 31-week study of rats that received a dietary supplement containing 20% wheat bran during administration of a carcinogen for 13 weeks when compared to rats that received a control diet. Rats that received the wheat bran after carcinogen exposure had a reduced number for benign adenomas when compared to controls. Wheat sprout extract (0.1 ml) was not an initiator or a promoter in mice that received the extract subcutaneously, were induced with DMBA, and/or promoted with croton oil in a 24-week study.

Anti-tumorigenic effects have been reported in an oral study with wheatgrass extract (20 ml/kg bw) in mice that were induced with DMBA and promoted with croton oil.

No irritation or sensitization was observed during an HRIPT of a face and body powder containing 13% Triticum Vulgare (Wheat) Germ Extract that was conducted in 105 subjects.

Work-related sensitization has been reported in bakery workers. Symptoms include rhinitis, asthma, contact urticaria, and hand eczema.

No relevant ocular irritation studies on wheat-derived ingredients were found in the published literature, and no unpublished data were provided. No relevant toxicokinetic studies were found in the published literature; however, in general, toxicokinetics data are not expected to be found on botanical ingredients because each botanical ingredient is a complex mixture of constituents.

INFORMATION SOUGHT

The CIR is seeking information regarding physical properties, method of manufacturing, and additional data on the composition and impurities of the wheat-derived ingredients as used in cosmetic formulations, as there may be a difference in constituent levels of different extracts. Clarification is specifically desired about the differences in compositions/impurities between the different wheat species, nomenclature equivalents, and the multiple names for certain plant parts (i.e. kernel, seed, and grain). Additional toxicological data, specifically dermal irritation and sensitization data on these cosmetic ingredients at maximum use concentrations, are especially being sought in order to help the CIR Expert Panel assess the safety of the use of these ingredients in cosmetics.

TABLES

Table 1. Definitions and functions of the ingredients in this safety assessment.[1]

Ingredient/CAS No.	Definition	Function
Triticum Aestivum (Wheat) Flour Lipids	Triticum Aestivum (Wheat) Flour Lipids is a mixture of lipids derived from the flour of *Triticum aestivum*.	Skin-conditioning agent – misc.
Triticum Aestivum (Wheat) Germ Extract	Triticum Aestivum (Wheat) Germ Extract is the extract of the germs of *Triticum aestivum*.	Antioxidant; skin-conditioning agent – misc.
Triticum Aestivum (Wheat) Leaf Extract	Triticum Aestivum (Wheat) Leaf Extract is the extract of the leaves of the wheat, *Triticum aestivum*.	Antioxidant
Triticum Aestivum (Wheat) Peptide	Triticum Aestivum (Wheat) Peptide is the di-/tri-peptide fraction isolated from the protein of *Triticum aestivum* by ultra-membrane filtration.	Film former; hair conditioning agent; skin-conditioning agent – misc.
Triticum Aestivum (Wheat) Seed Extract	Triticum Aestivum (Wheat) Seed Extract is the extract of the seeds of the wheat, *Triticum aestivum*.	Hair conditioning agent; skin-conditioning agent – misc.
Triticum Monococcum (Wheat) Seed Extract	Triticum Monococcum (Wheat) Seed Extract is the extract of the seeds of the wheat, *Triticum monococcum*. [*Triticum monococcum* is also known as eikorn and is native to eastern Europe and western Asia].[10]	Skin-conditioning agent – misc.
Triticum Monococcum (Wheat) Stem Water	Triticum Monococcum (Wheat) Stem Water is the aqueous solution of the steam distillates obtained from the stems of *Triticum monococcum.*	Flavoring agent
Triticum Spelta Seed Water	Triticum Spelta Seed Water is the aqueous solution of the steam distillates obtained from the seeds of *Triticum spelta*. *	Skin-conditioning agent – misc.
Triticum Turgidum Durum (Wheat) Seed Extract	Triticum Turgidum Durum (Wheat) Seed Extract is the extract of the seeds of *Triticum turgidum durum*.	Skin-conditioning agent – misc.
Triticum Vulgare/Aestivum (Wheat) Grain Extract	Triticum Vulgare/Aestivum (Wheat) Grain Extract is the extract of the grains of *Triticum vulgare* and *Triticum aestivum*.	Hair conditioning agent; skin-conditioning agent – misc.
Triticum Vulgare (Wheat) Bran	Triticum Vulgare (Wheat) Bran is the broken coat material of grains of wheat, *Triticum vulgare*.*	Abrasive; bulking agent
Triticum Vulgare (Wheat) Bran Extract 84012-44-2	Triticum Vulgare (Wheat) Bran Extract is the extract of the bran of *Triticum vulgare*.*	Skin-conditioning agent – misc.
Triticum Vulgare (Wheat) Bran Lipids	Triticum Vulgare (Wheat) Bran Lipids is the cyclohexane extract of Triticum Vulgare (Wheat) Bran.*	Skin-conditioning agent - occlusive
Triticum Vulgare (Wheat) Flour Extract	Triticum Vulgare (Wheat) Flour Extract is the extract of the powder obtained by grinding wheat, *Triticum vulgare*.*	Skin-conditioning agent – misc.
Triticum Vulgare (Wheat) Flour Lipids	Triticum Vulgare (Wheat) Flour Lipids is a mixture of lipids derived from the flour of *Triticum vulgare*.*	Skin-conditioning agent – misc.
Triticum Vulgare (Wheat) Germ	Triticum Vulgare (Wheat) Germ is the natural product obtained from the embryo of the wheat kernel separated in milling.*	Skin-conditioning agent – misc.
Triticum Vulgare (Wheat) Germ Extract 84012-44-2	Triticum Vulgare (Wheat) Germ Extract is the extract of the germ of *Triticum vulgare*.*	Skin bleaching agent; skin-conditioning agent – misc.
Triticum Vulgare (Wheat) Germ Powder	Triticum Vulgare (Wheat) Germ Powder is the powder obtained from the dried, ground wheat germ, *Triticum vulgare*.*	Abrasive; absorbent; bulking agent; viscosity increasing agent - aqueous
Triticum Vulgare (Wheat) Germ Protein	Triticum Vulgare (Wheat) Germ Protein is a protein obtained from the germ of the wheat, *Triticum vulgare*.*	Hair conditioning agent; skin-conditioning agent – misc.

Table 1. Definitions and functions of the ingredients in this safety assessment.[1]

Ingredient/CAS No.	Definition	Function
Triticum Vulgare (Wheat) Kernel Flour	Triticum Vulgare (Wheat) Kernel Flour is the milled flour obtained from the finely ground kernels of wheat, *Triticum vulgare*.*	Abrasive; bulking agent; viscosity increasing agent - aqueous
Triticum Vulgare (Wheat) Protein	Triticum Vulgare (Wheat) Protein is a protein obtained from wheat, *Triticum vulgare*.*	Film former; hair conditioning agent; skin-conditioning agent – misc.
Triticum Vulgare (Wheat) Seed Extract 84012-44-2	Triticum Vulgare (Wheat) Seed Extract is the extract of the seeds of *Triticum vulgare*.*	Skin-conditioning agent – misc.
Triticum Vulgare (Wheat) Sprout Extract	Triticum Vulgare (Wheat) Sprout Extract is the extract of the young shoots of *Triticum vulgare*.*	Skin-conditioning agent – misc.
Triticum Vulgare (Wheat) Straw Water	Triticum Vulgare (Wheat) Straw Water is the aqueous solution of the steam distillates obtained from *Triticum vulgare* (wheat) straw.*	Skin-conditioning agent – misc.

* The accepted scientific name for both *Triticum vulgare* and *Triticum spelta* is *Triticum aestivum*.[1]

Table 2. Generic plant part definitions as they apply to wheat-derived ingredients.[1]

Plant Part	Definition
Adventitious root	Secondarily produced roots that grow from non-root organs.
Bran	The outer hard layers of the grain formed by the fused fruit and seed wall in grains and cereals.
Endosperm	Energy storage tissue inside seeds.
Germ	The embryo in a seed; the part of a seed that can develop into new plant.
Grain	Dry one-seeded fruits produced by grasses, e.g. cereals such as wheat.
Kernel	The grain of a grass.
Leaf	Flattened photosynthetic organs, attached to stems.
Pericarp	Fruit wall.
Root	Organ of a plant that absorbs and transports water and nutrients, lacks leaves and nodes, usually underground
Seed	A propagating sexual structure resulting from the fertilization of an ovule, formed by embryo, endosperm, or seed coat.
Seed coat	Seed wall; testa; protective outer layer of seed, formed from the outer layers of the ovule
Sprout	Seedling; germinating seed; any new growth of a plant from a stem such as a new branch or a bud
Stem	A slender or elongated structure that supports a plant or a plant part or plant organ.
Straw	The stem of a grass or related families

Table 3. Frequency (2019) and concentration of use (2017) according to duration and type of exposure for *Triticum aestivum* (Wheat)-derived ingredients[24,25]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Triticum Aestivum (Wheat) Flour Lipids		**Triticum Aestivum (Wheat) Germ Extract**		**Triticum Aestivum (Wheat) Seed Extract**		**Triticum Monococcum (Wheat) Seed Extract**	
Totals†	**16**	**NR**	**284**	**0.0002-0.6**	**160**	**NR**	**3**	**NR**
Duration of Use								
Leave-On	12	NR	240	0.0002-0.6	115	NR	2	NR
Rinse Off	4	NR	44	NR	44	NR	1	NR
Diluted for (Bath) Use	NR	NR	NR	NR	1	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	39	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	18	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1; 7[a]; 4[b]	NR	2; 71[a]; 70[b]	NR	7; 78[a]; 22[b]	NR	2[a]	NR
Incidental Inhalation-Powder	4[b]	NR	7; 70[b]	0.0002[c]	22[b]	NR	NR	NR
Dermal Contact	7	NR	246	0.0002-0.6	151	NR	3	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	9	NR	20	NR	9	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	20	NR	23	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Triticum Vulgare (Wheat) Bran[e]		**Triticum Vulgare (Wheat) Bran Extract[e]**		**Triticum Vulgare (Wheat) Bran Lipids[e]**		**Triticum Vulgare (Wheat) Flour Extract[e]**	
Totals†	**21**	**0.2-0.61**	**69**	**0.005-0.05**	**2**	**NS**	**2**	NR
Duration of Use								
Leave-On	20	NR	62	0.005-0.05	2	NS	NR	NR
Rinse Off	1	0.2-0.61	7	NR	NR	NS	2	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NS	NR	NR
Exposure Type								
Eye Area	2	NR	7	0.02	NR	NS	NR	NR
Incidental Ingestion	NR	NR	10	0.015	NR	NS	NR	NR
Incidental Inhalation-Spray	3[a]; 12[b]	NR	28[a]; 12[b]	0.02[a]	NR	NS	NR	NR
Incidental Inhalation-Powder	12[b]	NR	1; 12[b]	0.025-0.05[c]	NR	NS	NR	NR
Dermal Contact	20	0.2-0.61	57	0.005-0.05	NR	NS	2	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NS	NR	NR
Hair - Non-Coloring	1	NR	2	0.01	NR	NS	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NS	NR	NR
Nail	NR	NR	NR	NR	NR	NS	NR	NR
Mucous Membrane	1	0.2-0.61	11	0.015	NR	NS	NR	NR
Baby Products	NR	NR	NR	NR	NR	NS	NR	NR

Table 3. Frequency (2019) and concentration of use (2017) according to duration and type of exposure for *Triticum aestivum* (Wheat)-derived ingredients[24,25]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Triticum Vulgare (Wheat) Flour Lipids[e]		**Triticum Vulgare (Wheat) Germ**		**Triticum Vulgare (Wheat) Germ Extract***		**Triticum Vulgare (Wheat) Germ Protein[e]**	
Totals[†]	**NR**	**0.00065-0.1**	**5**	**NR**	**40**	**0.00001-13**	**60**	**0.0015-0.03**
Duration of Use								
Leave-On	NR	0.00065-0.1	4	NR	35	0.00001-13	12	0.0015-0.03
Rinse Off	NR	NR	1	NR	5	0.001-0.32	48	0.0075
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	0.00065	NR	NR	2	0.004-0.075	1	0.0075-0.01
Incidental Ingestion	NR	NR	NR	NR	NR	0.13	NR	NR
Incidental Inhalation-Spray	NR	0.05[a]	3[b]	NR	19[a]; 9[b]	0.005-0.32; 0.0012-0.025[a]; 0.02[b]	2[a]; 7[b]	NR
Incidental Inhalation-Powder	NR	0.1[c]	3[b]	NR	9[b]	13; 0.02[b]; 0.0001-0.2[c]	7[b]	0.015; 0.0075-0.03[c]
Dermal Contact	NR	0.05-0.1	5	NR	37	0.00001-13	13	0.0075-0.03
Deodorant (underarm)	NR	NR	NR	NR	NR	0.1-0.11[d]	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	2	0.001-0.32	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	46	NR
Nail	NR	NR	NR	NR	NR	NR	1	0.0015
Mucous Membrane	NR	NR	NR	NR	NR	0.1-0.13	1	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Triticum Vulgare (Wheat) Kernel Flour[e]		**Triticum Vulgare (Wheat) Protein[e]**		**Triticum Vulgare (Wheat) Seed Extract**		**Triticum Vulgare (Wheat) Sprout Extract[e]**	
Totals[†]	**4**	**NS**	**95**	**0.01-0.16**	**NR**	**0.34**	13	NR
Duration of Use								
Leave-On	2	NS	78	0.01-0.16	NR	0.34	11	NR
Rinse Off	2	NS	17	NR	NR	NR	2	NR
Diluted for (Bath) Use	NR	NS	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NS	17	0.16	NR	NR	1	NR
Incidental Ingestion	NR	NS	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1[b]	NS	1; 7[a]; 35[b]	NR	NR	NR	2[a]; 5[b]	NR
Incidental Inhalation-Powder	1[b]	NS	35[b]	NR	NR	0.34[c]	5[b]; 2[c]	NR
Dermal Contact	4	NS	77	0.16	NR	0.34	11	NR
Deodorant (underarm)	NR	NS	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NS	17	NR	NR	NR	1	NR
Hair-Coloring	NR	NS	NR	NR	NR	NR	1	NR
Nail	NR	NS	NR	0.01	NR	NR	NR	NR
Mucous Membrane	1	NS	1	NR	NR	NR	NR	NR
Baby Products	NR	NS	NR	NR	NR	NR	3	NR

NR = Not reported; NS = Not yet surveyed

† Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

* VCRP data was listed generically as Wheat Germ Extract

a. It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

b. Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

c. It is possible these products may be powders, but it is not specified whether the reported uses are powders.

d. 0.11% in a spray deodorant

e. Listed with the nomenclature Triticum Aestivum in the VCRP database.

Table 4. Ingredients not reported to be in use.[24,25]

Triticum Aestivum (Wheat) Leaf Extract
Triticum Aestivum (Wheat) Peptide
Triticum Monococcum (Wheat) Stem Water
Triticum Spelta Seed Water*
Triticum Turgidum Durum (Wheat) Seed Extract
Triticum Vulgare/Aestivum (Wheat) Grain Extract
Triticum Vulgare (Wheat) Germ Powder
Triticum Vulgare (Wheat) Straw Water

*Concentration of use not yet surveyed by the Council.

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