United States Department of Agriculture
Agricultural Marketing Service | National Organic Program
Document Cover Sheet
https://www.ams.usda.gov/rules-regulations/organic/petitioned-substances

Document Type:

☐ **National List Petition or Petition Update**

A petition is a request to amend the USDA National Organic Program's National List of Allowed and Prohibited Substances (National List).

Any person may submit a petition to have a substance evaluated by the National Organic Standards Board (7 CFR 205.607(a)).

Guidelines for submitting a petition are available in the NOP Handbook as NOP 3011, National List Petition Guidelines.

Petitions are posted for the public on the NOP website for Petitioned Substances.

☒ **Technical Report**

A technical report is developed in response to a petition to amend the National List. Reports are also developed to assist in the review of substances that are already on the National List.

Technical reports are completed by third-party contractors and are available to the public on the NOP website for Petitioned Substances.

Contractor names and dates completed are available in the report.

Rye Pollen Extracts

Handling/Processing

Identification of Petitioned Substance

Chemical Names:
lipid-soluble rye pollen extract; phenolic mixture of gallic acid, chlorogenic acid, rutin, quercetin, and carvacrol; water-soluble rye pollen extract.

Other Names:
Secale cereale pollen extract.

Trade Names:
Cernitin; Cernitol; Cernilton; Flower Pollen Extract; Graminex G60; Graminex NAX; Pollitin.

CAS Numbers:
n/a

Other Codes:
n/a

Summary of Petitioned Use

This full scope technical report provides information to the National Organic Standards Board (NOSB) in support of its review of rye pollen extracts. In August 2022, Graminex, L.L.C. submitted a petition (Graminex, LLC, 2022) for rye pollen extracts to be included as a handling material on the National List of Allowed and Prohibited Substances (hereafter referred to as "The National List"). The petitioner requested that two varieties of rye pollen extract be included at 7 CFR 205.606 as permitted nonorganically produced agricultural products used in products labeled as "organic":

Pollen extracts (*Secale cereale*)

1. Water-soluble pollen extract (Water extraction)
2. Lipid-soluble pollen extract (Supercritical CO_2 extraction)

The petition focuses on the uses of rye pollen extracts as components of vegan honey substitutes intended to mimic the characteristics of bee honey (Graminex, LLC, 2022). According to the petitioner, organic sources of the specific high-pollen-producing rye variety needed for the production of extracts are unavailable (Graminex, LLC, 2022).

Rye pollen extracts comprise a complex mixture of carbohydrates, minerals, proteins, amino acids, vitamins, lipids, organic acids, and phenolic compounds (Graminex, LLC, 2022; Locatelli et al., 2018). As such, they are not identified by discrete Chemical Abstracts Service (CAS) Registry Numbers.

Unless otherwise specified, the petitioned rye pollen extracts will be referred to as RPE in this report.

Characterization of Petitioned Substance

Composition of the Substance:
In general, pollen (from flowers or bee sources) typically contains variable levels of vitamins A, C, E, B_1 (thiamine), B_2 (riboflavin), B_3 (niacin), B_5 (pantothenic acid), B_6 (pyridoxine), B_7 (biotin), B_9 (folic acid), and the minerals potassium, phosphorus, calcium, magnesium, zinc, manganese, iron, and copper (Antonelli et al., 2019). Pollen also contains proteins, amino acids, carbohydrates, lipids, and fatty acids (El Ghouizi et al., 2023; Kostić et al., 2020). The petitioned materials are specifically extracted from flower pollen. Bee pollen extracts are not included in the petition, although there are some similarities in the overall composition.[1]

[1] Bee pollen is a mixture of flower pollen collected by bees and carried to the hive in pollen baskets on their rear legs. Bees agglutinate pollen together by chewing with small amounts of saliva, enzymes, nectar, or honey, whereas flower pollen is the individual pollen grains directly produced from the reproductive organs of plants (Denisow & Denisow-Pietrzyk, 2016; Rzepecka-Stojko et al., 2015). Bees transform nectar into honey in their guts, which involves filtering out residual pollen in specialized organs (Bryant, 2020).

Much of the available literature on the composition of grass pollen (family Poaceae, formerly Gramineae) focuses on the allergenic potential of inhalable particles. The highly allergenic timothy grass (*Phleum pretense)* often serves as a model in studies related to grass allergies and the chemical composition of grass pollen grains (Visez et al., 2021). Similarities exist within the chemical profiles of rye pollen, timothy grass pollen, and ragweed pollen (Johnson & Marsh, 1966). For example, each rye pollen grain contains an estimated 700-1000 starch granules within the cytoplasm, which is similar in number and volume to timothy grass pollen (Visez et al., 2021). Using timothy grass as a model, Visez et al. (2021) include the following as the major chemical components of pollen grains:

- sporopollenin (a component of the outside wall of pollen grains)
- sugars
- polysaccharides
- starch
- glycoproteins (which include the major allergenic compounds)
- amino acids
- lipids
- flavonoids
- phenolic compounds
- phytoprostanoids
- carotenoids
- absorbed pollutants
- silicon
- magnesium
- calcium

Morgia and Privitera (2018) state that amino acids, enzymes, coenzymes, sterols, minerals, trace elements, and all known vitamins occur specifically in RPE. Phytosterols and fatty acids, including alpha linoleic-acid, have been detected in the fraction soluble in acetone (Morgia & Privitera, 2018).

Much of the available literature focuses on the therapeutic effects for humans of phenolic compounds present in pollen.[2] Plants produce phenolic compounds (sometimes referred to as polyphenols) as a defense mechanism, or as chemical signals (Lattanzio, 2013). Although not directly essential for plant photosynthesis and respiration, phenolic compounds serve important roles in plant survival and stress response (Bennett & Wallsgrove, 1994; Lattanzio, 2013). The group of compounds not related to essential physiological function are known as secondary metabolites. Phenolic compounds are secondary metabolites that can affect odor, taste, and color, making plant tissues less palatable to discourage herbivory (Bennett & Wallsgrove, 1994; Lattanzio, 2013).

Locatelli et al. (2018) analyzed a sample of Graminex (a rye pollen extract product, produced by the petitioner) in a study exploring its anti-inflammatory and antioxidant effects in rat prostate tissue, focusing on the phenolic compound profile. The researchers describe the sample as a mixture of rye, corn, and timothy pollen. Using high performance liquid chromatography methods (HPLC), they detected a phenolic mixture of secondary metabolites including gallic acid, chlorogenic acid, rutin, quercetin, and carvacrol (Locatelli et al., 2018).

Visez et al. (2021) state that despite the critical role they play in plant reproduction and human allergic potential, the specific chemical composition of pollen grains remains largely unknown. However, Johnson and Marsh (1966) provide an amino acid profile detected in skin-active rye pollen allergens:

- lysine
- histidine
- arginine
- aspartic acid
- threonine
- serine

[2] Phenolic compounds can be generically described as chemicals bearing one or more six carbon rings (phenyl rings) and one or more hydroxyl groups (Lattanzio, 2013).

- glutamic acid
- proline
- glycine
- alanine
- cysteine
- valine
- methionine
- isoleucine
- leucine
- tyrosine
- phenylalanine
- tryptophan

<u>Source or Origin of the Substance:</u>

Wild rye, wheat, and barley share a common ancestor thought to have originated in western Asia (Martis et al., 2013). Wild rye diverged from barley 11 million years ago and from wheat 7 million years ago (Martis et al., 2013). It was domesticated 7,000 years ago in modern Turkey and Eastern Europe, later than the agricultural revolution "founder" crops wheat, barley, peas, vetch, and lentils (Martis et al., 2013; Schreiber et al., 2021).

People sometimes confuse cereal rye (*Secale cereale*) and annual or perennial ryegrass (*Lolium perenne*) because of the similarity in name (Rice, 2022; USDA Natural Resources Conservation Service, 2022). While both species are in the Poaceae family of grasses, they have different growth habits and environmental tolerances. Both are commonly used as cover crops (Rice, 2022). This report focuses on pollen from cereal rye.

While not nearly as common as wheat, rye is cultivated on six continents, even in cold and arid environments, tropical or subtropical climes, and at high elevations (Schreiber et al., 2021). Rye is particularly tolerant to drought, salinity, and aluminum stress, and exceeds other cereal grains in its ability to overwinter (Geiger & Miedaner, 2009). Rye tolerates extreme climates and low quality soils better than its relatives (Schreiber et al., 2021). This has led to its greater prevalence as a cereal crop in northern latitudes (Schreiber et al., 2021). The majority of global production (75%) occurs in Russia, Belarus, Poland, Germany, and Ukraine (Geiger & Miedaner, 2009). In 2020, over 15 million metric tons of rye were grown on approximately 11 million acres (Brzozowski et al., 2023).

Rye is naturally monoecious (Polanco et al., 1994), meaning it has both male and female flower parts. Like many other grass species, *Secale cereale* rye is self-incompatible, meaning it is incapable of self-fertilization (Baumann et al., 2000; Slatter et al., 2020). Self-incompatibility is a trait of many flowering plants that prevents inbreeding (Slatter et al., 2020). This increases genetic diversity in the population, and facilitates greater resilience to environmental changes (Slatter et al., 2020). However, grasses are known to genetically mutate into self-pollinating varieties in wild and agricultural settings, including *Secale cereale* rye (Slatter et al., 2020). Plant breeders have been able to produce self-fertilizing grasses by exploiting genetic traits of certain hybrid mutants (Slatter et al., 2020).

Most modern rye varieties are hybrids, developed by breeders using genic male sterility mechanisms (Geiger & Miedaner, 2009). Hybrids are produced when two different crop varieties are bred together, often leading to progeny with enhanced vigor (Eckardt, 2006; Islam et al., 2014).

Fertile rye produces a large volume of pollen with the ability to travel long distances, so extreme care is required in breeding programs since any genetic contamination leading to sterility can render an entire crop useless for future seed production (Geiger & Miedaner, 2009). When producing hybrids, breeders sometimes use plants of one variety that are functionally female to provide added control to the mating process (Islam et al., 2014). These functionally female plants have a trait called "cytoplasmic male sterility" or CMS (Stojałowski et al., 2004; Eckardt, 2006). In CMS, maternally inherited mitochondria that live in the cytoplasm contain genetic mutations that lead to the inability to produce pollen (Stojałowski et al., 2004; Eckardt, 2006; Cheng et al., 2023).

The petitioner states that organic breeding stock with high pollen-producing potential is commercially unavailable, despite the availability of organic rye. Breeding goals and challenges help explain why this may be. The common goal in most rye breeding is grain yield rather than pollen production (Geiger & Miedaner, 2009). In order to restore fertility in rye breeding lines, plant breeders must carefully backcross hybrid and inbred varieties to produce viable parents (Geiger & Miedaner, 2009). Fertility restoring efforts are often unsuccessful and result in hybrids with reduced pollen shedding (Geiger & Miedaner, 2009).

<u>Properties of the Substance:</u>
The petitioner describes the water-soluble fraction of RPE as a beige, fine, hygroscopic powder with a slightly acidic taste and hay-like odor (Graminex, LLC, 2022). They describe the lipid-soluble fraction as a dark, greenish-brown to almost black hygroscopic oily paste with a bitter and acidic taste and a hay-like odor (Graminex, LLC, 2022).

The vast majority of the available literature on grass pollen extracts focuses on phytotherapy, or the use of plants to relieve symptoms related to disease. These studies typically do not describe the physical properties of the substance. In the research for this report, we found no explicit physical descriptions of RPE raw material used in food products except that found in the petition. As therapeutic products, RPE may be mixed with several excipients and encapsulated.

<u>Specific Uses of the Substance:</u>
The petitioner of RPE indicated its use is as a functional ingredient in vegan syrups intended as a honey alternative (Graminex, LLC, 2022). Functional ingredients are ingredients in food that provide added physiological benefits beyond their basic nutrition (Day et al., 2009). The petition recommends the use of 500 mg of water-soluble pollen extract per eight oz. of syrup, or 25 mg of the lipid-soluble form (Graminex, LLC, 2022). The Safety Data Sheet provided with the petition identifies the following product uses (Graminex, LLC, 2022):

- dietary supplements
- nutraceuticals
- pharmaceuticals
- functional foods and beverages
- cosmetics

As a functional ingredient, RPE provides not only nutrient vitamins and minerals, omega-3, 6, and 9 fatty acids, and other phytonutrients, but also biologically active components such as enzymes, polyphenols and phytosterols (Graminex, LLC, 2022). Rye is one of the most common plant species from which humans directly collect pollen, along with corn (*Zea mays*) and timothy (*Phleum pretense*) (Antonelli et al., 2019). Flower pollen extracts like rye are used for managing symptoms of prostate disorders and for immunotherapies (Antonelli et al., 2019). However, we found no literature documenting use of RPE as a food supplement or ingredient. In contrast, there is extensive literature on the dietary uses of bee pollen (Almeida et al., 2017; El Ghouizi et al., 2023; Kostić et al., 2020), including for use in livestock feed (Haefeker, 2021).

Biological activity
Like other botanical extracts, all pollens present a complex mixture of compounds, some of which are biologically active (Mora, 2022). Biologically active compounds occur in small quantities in food and can have health benefits beyond just providing nutritional value when consumed (Santos et al., 2019). The biologically active components of pollen are what make it a functional ingredient. In pollen, biologically active components include phenolic compounds such as flavonoids, carotenoids (e.g., lutein, β-cryptoxanthin, and β-caroten) and tannins, phytosterols, and enzymes such as superoxide dismutase (SOD) mimics (Mora, 2022).

These biologically active compounds make pollen, in general, an effective antioxidant (Almeida et al., 2017). Food processors include bee pollen as an ingredient for this purpose in meat preservation and other food products to limit discoloration and off flavors resulting from oxidation (Almeida et al., 2017; Anjos et al., 2019; Dundar, 2022). Researchers have found that the extraction method used to obtain the pollen impacts its efficacy as an antioxidant (Borycka et al., 2015; Kroyer & Hegedus, 2001). Researchers have also documented antibacterial effects of pollen (Borycka et al., 2015; Çobanoğlu et al., 2023; Denisow & Denisow-Pietrzyk, 2016; Velásquez et al., 2023).

Therapeutic treatment
The most well documented therapeutic uses of rye pollen extract include treatments for:

- chronic prostatitis (CP) (Antonelli et al., 2019; Cai, Verze, La Rocca, Palmieri, et al., 2017)
- lower urinary tract symptoms (LUTS) in men with benign prostate hyperplasia (BPH) (Altarac et al., 2010; Antonelli et al., 2019; Espinosa & Esposito, 2020)
- pelvic inflammatory disease (PID) (Chiavaroli et al., 2022)
- chronic pelvic pain syndrome (Cai, Verze, La Rocca, Anceschi, et al., 2017)
- radiation-induced prostatitis (NIH-National Cancer Institute, 2017)

Several reports attribute other therapeutic benefits to the biologically active components in pollen. These include anti-carcinogenic (Aylanc et al., 2023; Kostić et al., 2020), anti-inflammatory, antidiabetic, and anti-hyperglycemic properties (El Ghouizi et al., 2023). Kostić et al. (2020) also suggest hepatoprotective and cardioprotective functions of pollen.

Other therapeutic uses include treatment for symptoms associated with menopause (Mora, 2022; Winter et al., 2002), including vasomotor symptoms in women (Antonelli et al., 2019; Kostić et al., 2020).

Approved Legal Uses of the Substance:
As petitioned, RPE is used as an ingredient in vegan honey substitutes (Graminex, LLC, 2022). As a food ingredient, the FDA regulates the use of RPE.

The FDA requires manufacturers of substances that have not previously been used in dietary supplements (known as "new dietary ingredients," or NDIs) to submit a premarket safety notification at least 75 days before introducing the product into interstate commerce (U.S. Department of Health and Human Services et al., 2022). Substances used in dietary supplements that were marketed in the United States prior to October 15, 1994 are not considered NDIs, and are not subject to the premarket notification requirement (U.S. Department of Health and Human Services et al., 2016). When used as an ingredient in a dietary supplement, the rye pollen extract manufactured by Graminex L.L.C. is exempt from the requirement of the premarket notification because it was marketed prior to October 15, 1994 (Graminex, LLC, 2022; U.S. Department of Health and Human Services et al., 2016).

The FDA exempts cultivated rye grass (*Secale cereale*) from premarket notification to the FDA when used in immunological test systems for the diagnosis of asthma, allergies, and other pulmonary disorders at 21 CFR 866.5750.

The Graminex, L.L.C. facility located in Deshler, OH, is certified by NSF International to NSF/ANSI 455-2 Good Manufacturing Practices for Dietary Supplements. NSF/ANSI 455-2 includes requirements from 21 CFR part 111, 21 CFR part 117, 21 CFR part 11, 21 CFR part 1.5 subpart L, and 21 CFR part 1.9 subpart O (NSF International, 2023).

Action of the Substance:

Source of nutrients for vegan honey substitutes
As petitioned, RPE adds pollen to vegan honey substitutes, helping to provide the nutrient profile of honey without the use of animal products derived from bees (Graminex, LLC, 2022).

Although many honeys are marketed as specific floral varieties, beekeepers are often incorrect in their identifications of flower nectar sources because they only determine the source by observation of nearby plants (Bryant, 2020). Honey commonly contains pollen from the nectar source plant, but also contains errant pollen stuck to bees or windblown into the hive. Bees are also more efficient at removing larger pollen grains than smaller pollen grains from collected nectar during the filtering process occurring inside their gut, meaning that identification of the resulting honey's source plant(s) may be skewed. Furthermore, many commercial honeys are filtered or processed so there is essentially no pollen remaining (Bryant, 2020).

Pollen contains high concentrations of vitamins, minerals, and nutrients (Antonelli et al., 2019). However, according to the National Honey Board (2023), the amount of pollen in honey is so small as to not provide any nutritive value to those that consume it.

Action for other uses - phytotherapeutic treatments
Most of the available literature focuses on the mode of action of pollen extracts as phytotherapeutic treatments for urological issues, symptoms related to hormones, and responses to cancer treatments. The mode of action in phytotherapeutic capacities is thought to be related to the anti-inflammatory, antioxidant, antimicrobial, and antiallergenic activities of polyphenols and flavonoids which are concentrated in the extracts (Antonelli et al., 2019; Denisow & Denisow-Pietrzyk, 2016; Locatelli et al., 2018; Rzepecka-Stojko et al., 2015). Polyphenols scavenge reactive oxygen species and inactivate organic radicals which may prevent oxidative damage in cells (Rzepecka-Stojko et al., 2015). Although Rzepecka-Stojko et al. (2015) specifically focused on bee pollen in their study of the phytotherapeutic mode of action, polyphenols are a component of pollen itself and not a result of bee activity (Denisow & Denisow-Pietrzyk, 2016). Campos et al. (2010) state that bees contribute a minor amount of nutritive constituents to bee pollen, mostly consisting of soluble carbohydrates like glucose and fructose. Roulston and Cane (2000) state that the volume of added sugars contributed by bees to collected pollen is uncertain, however.

Combinations of the Substance:
The petition for RPE identifies maltodextrin as a carrier for the water extract, added prior to spray drying. The lipid-soluble extract contains no added ingredients (Graminex, LLC, 2022).

As a pharmaceutical and dietary supplement formulation in capsule form, the product labels for RPE consulted for this report describe numerous excipient ingredients, such as microcrystalline cellulose, calcium hydrogen phosphate dihydrate, calcium gluconate, and silicon dioxide (Amazon.com, Inc., n.d.).[3] Excipients may also include cellulose, magnesium stearate, and talc (Mora, 2022). Formulators of therapeutic RPE products may also combine the pollen extract with other therapeutic actives including extract of grass pistils, royal jelly, and DL-alpha tocopherol (Winter et al., 2002).

Status

Historic Use:
The cultivation of rye for food goes back centuries, as does the knowledge of pollen as food (Kostić et al., 2020). However, the specific use of a water- or lipid-soluble extract from rye pollen for use as a functional ingredient in food is relatively new. We did not find any documentation of it in the literature.

The term "pollen" dates back to the 1600s and originates from the Latin word for flour, suggesting its recognition as food (Kostić et al., 2020). Antonelli et al. (2019) cite the period after World War II as the time when people began isolating pollen and using it as a supplement and therapeutic remedy. This was due to the development of new technologies that facilitated its collection, such as bee pollen traps and, subsequently, mechanized flower pollen collectors (Antonelli et al., 2019). The new access to pollen for food

[3] Although the NOP specifically refers to "excipients" only in relation to livestock health care substances, the term is customarily used to refer to inactive substances in medical or supplement formulations alongside an active ingredient. "Ancillary substance" may be a more conventionally used term in the context of ingredients used in organic products.

supplement and health purposes spurred scientific research into these applications. Kostić et al. (2020) noted that scientists first presented reviews of pollen as a food ingredient in the 1970s.

Pollen extraction, versus simple collection, is a more recent phenomenon and is performed to better access the nutrients and bioactive compounds in pollen by first removing the outer layer of the pollen (Antonelli et al., 2019). The poorly-digestible outer layer of the pollen is both a barrier to the bio accessibility of beneficial compounds and is potentially allergenic (Mora, 2022). Thus, formulators of supplements and therapies find it advantageous to eliminate the outer pollen layer through extraction. Two patents published in the 2000s describe methods for extracting, standardizing, and preparing pollen extracts from grass plants, including rye (Mora, 2022; Winter et al., 2002). Both are for therapeutic treatments to alleviate symptoms of disease. Espinosa and Esposito (2020) note that RPE has been used to treat urinary and prostate issues for over 35 years in Europe under the brand name Cernilton.

Organic Foods Production Act, USDA Final Rule:

Rye, rye pollen, and rye pollen extract do not appear in the OFPA (Organic Foods Production Act of 1990, 1990).

7 CFR 205.301(b) permits certain nonorganically produced ingredients (that are listed at 7 CFR 205.606) at less than 5% of a product's formulation when not commercially available in organic form, quality, or quantity. Rye pollen extract does not appear at 7 CFR 205.606 and therefore must be certified organic when used as an ingredient in products labeled as "organic."

International

None of the following organic standards specifically identify extracts of plant pollen as allowed nonorganic substances. In general, the allowance for nonorganic ingredients used in processed organic food is subject to commercial availability searches.

Canada, Canadian General Standards Board – CAN/CGSB-32.311-2020, Organic Production Systems Permitted Substances List

CAN/CGSB-32.311 contains no reference to RPE or other plant pollen extracts on the Permitted Substances List (PSL) Tables 6.3 (*Ingredients classified as food additives*), 6.4 (*Ingredients not classified as food additives*) or 6.5 (*Processing Aids*). However, RPEs could be allowed as nonorganic agricultural ingredients. These are allowed in different quantities, depending on the organic category:

- Per CAN/CGSB 32.310 9.2.1(d), nonorganic agricultural ingredients are allowed to be up to 5% of the product composition in "95% organic content (or more)" products. Commercial availability restrictions apply in this category.
- Per CAN/CGSB 32.310 9.2.2(a), nonorganic agricultural ingredients are allowed to be up to 30% of the product composition in "70-95% organic content" products. Commercial availability does not apply.

Nonorganic agricultural ingredients must meet the requirements of CAN/CGSB-32.310 1.4 a), 1.4 c) and 1.4 d), which means that they must not be produced using genetic engineering, irradiation, or cloned livestock.

RPEs are extracted with water and supercritical carbon dioxide. Carbon dioxide is listed on PSL Table 6.5 as an allowed processing aid. Extraction with water is allowed per CAN/CGSB 32.310 8.1.3.

Per CAN/CGSB-32.310 5.3, organic seed is required unless commercially unavailable, determined by a documented search of organic seed suppliers.

CODEX Alimentarius Commission – Guidelines for the Production, Processing, Labelling and Marketing of Organically Produced Foods (GL 32-1999)

CODEX guidelines do not mention RPE or other pollen extracts in any specific way. As guidelines rather than standards, CODEX does not enforce specific organic standards. Section 3.4 allows derogations for nonorganically produced agricultural ingredients at a maximum of 5% of the formulation, excluding salt and water.

European Economic Community (EEC) Council Regulation – EC No. 2018/848 and 2021/1165
Regulation EU 2018/848 on organic production and labelling of organic products requires agricultural ingredients in processed foods to be organic unless permitted by a restricted list appearing in EU 2021/1165.

Where organic ingredients are not available in sufficient quantity for the production of processed organic food, Member States may provisionally allow the use of nonorganic agricultural ingredients under certain conditions and for a maximum of six months, which may be extended twice at six months each extension, per Article 25 of EU 2018/848. After all extensions have been exhausted and the ingredient remains unavailable in organic form, Member States may request the Commission add the substance to the list of restricted non-organic agricultural ingredients used in processed organic food.

Annex V, Part B of EU 2021/1165 contains the relevant list of nonorganic agricultural ingredients authorized for use in the production of processed organic food. RPE does not appear on the list, nor does any other ingredient related to plant pollen.

Japan Agricultural Standard (JAS) for Organic Production
The Japan Agricultural Standard for Organic Production makes no mention of RPE or other plant pollen-related ingredients. The Standard for Organic Processed Foods, Article 4, permits the use of nonorganic plant-based ingredients only when organic products of plant origin are difficult to obtain.

IFOAM-Organics International
The IFOAM Norms only mention pollen in the section on beekeeping. Sources of pollen for bees must come from organically managed crops, uncultivated land, or wild natural areas. RPE is not included in the list of approved additives for human foods, nor is any other iteration of plant pollen-based material.

Evaluation Questions for Substances to be used in Organic Handling

<u>Evaluation Question #1:</u> Describe the most prevalent processes used to manufacture or formulate the petitioned substance. Further, describe any chemical change that may occur during manufacture or formulation of the petitioned substance when this substance is extracted from naturally occurring plant, animal, or mineral sources [7 U.S.C. 6502(21)].
The manufacturing processes described in the petition are somewhat limited in detail. Graminex, L.L.C. (Graminex, LLC, 2022) extracts one water-soluble fraction from rye pollen with water and another lipid-soluble fraction with supercritical carbon dioxide. Both fractions result from the same starting material, rye pollen, and their manufacturing processes only differ in the extraction step.

Graminex, L.L.C. harvests rye in the spring, taking the top 12-18 inches of the pollen-containing stalks (Graminex, LLC, 2022). The raw material is dried before the pollen is isolated through undescribed means. Water acts as the extractant for the water-soluble fraction and supercritical carbon dioxide works as the extractant for the lipid-soluble portion, but few details are provided about the extent of processing, or the specific methods or equipment used. The water-soluble fraction is spray-dried using maltodextrin as a carrier, while the lipid-soluble fraction contains no other ingredients (Graminex, LLC, 2022).

No explanation is provided by the petitioner on whether or not they use some process to break down the outer shell of the pollen wall. The few patents and articles available indicate that some level of digestion before extraction is beneficial or necessary to release the content of the cytoplasm (Gosta, 1967; Mora, 2022; Morgia & Privitera, 2018; Morra, 2019). Some preparations may involve microbial digestion of rye pollen prior to extraction with water and other solvents, resulting in water-soluble and acetone-soluble fractions (Morgia & Privitera, 2018).

The lipid-soluble fraction may also be extracted using organic solvents such as methylene chloride after grinding (Visez et al., 2021).

Given the dearth of pollen extract products, there is little information about the manufacture of these substances. Much of the available information relates to nutraceuticals and dietary supplements, largely for use in treatment of health issues or symptoms related to disease. We located several patents for nutraceutical or herbal medicine applications, most of which have been translated from Chinese and Japanese. The processes are generally not fundamentally different from the information provided in the petition except for the choice of solvents.

In a patent filed in 2022, Mora (2022) describes a variety of pollen and pistil extracts and their manufacturing processes in greater detail than that provided in the petition. The primary uses of these extracts are in pharmaceutical and food supplements for the management of symptoms related to menopause, premenstrual syndrome, premenstrual dysphoric disorder, and hormonal therapy related to cancer treatments. The starting materials are stand-alone or mixed blends of pollen extract from rye, corn, pine, and orchard grass, and extractants include water, glycerin, glycols, ethers, oils, alcohols, and ketones (Mora, 2022).

The patent describes optimal extraction and spray-drying temperatures, as well as optimal duration to reduce denaturing of the proteins in the pollen extracts (Mora, 2022). The described optimal temperature and time for extraction is 30-45 °C for 12-90 hours. The allergenic pollen husks are separated from the active substances in the cytoplasm by a separation step at 2,800 revolutions per minute, leading to extracts claimed to be without allergenic potential. The extracts are purified and concentrated by filtration and/or evaporation, followed by spray-drying. The final products are powders or liquids that are encapsulated or formed into tablets, some formulated with various excipients including microcrystalline cellulose, magnesium stearate, talc, and shellac (Mora, 2022).

Supercritical carbon dioxide extraction is similar to other organic solvent extractions but with lesser potential for contamination or carryover in the final product and the environment (Subramaniam et al., 1997). Carbon dioxide enters a supercritical state when subjected to pressures above 73 bar and temperatures above 31°C, and exhibits properties of a liquid and gas simultaneously, allowing it to penetrate substances like a gas while also flowing like a liquid solvent (Subramaniam et al., 1997). As a nonpolar solvent, supercritical carbon dioxide generally dissolves the same substances as hexane, a more commonly used organic solvent (Subramaniam et al., 1997).

The petition did not explain the specific supercritical carbon dioxide extraction process used for RPE. However, substantial literature is available on supercritical carbon dioxide extraction methods, and we would expect them to be relatively similar, particularly to flower pollen or bee pollen extraction methods.

In general terms, carbon dioxide is pumped through a refrigeration chamber and into another vessel as a pressurized liquid. The liquid carbon dioxide is then pumped through a heater to reach the supercritical temperature and percolated through a jacketed vessel containing the substance to be extracted. The nonpolar, lipid-soluble fraction is collected in cooling separators, allowing the carbon dioxide to cool below supercritical temperature again for recirculation. Some methods may simply depressurize the system and release the carbon dioxide as gas (Li et al., 2021; X. Wang et al., 2009; X. Xu et al., 2008, 2009, 2011).

<u>Evaluation Question #2:</u> Discuss whether the petitioned substance is formulated or manufactured by a chemical process or created by naturally occurring biological processes [7 U.S.C. 6502(21)]. Discuss whether the petitioned substance is derived from an agricultural source.

RPE is derived from an agricultural source. Evaluation of RPE against Guidance National Organic Program (NOP) 5033-2 *Decision Tree for Classification of Agricultural or Nonagricultural Materials for Organic Livestock Production and Handling* (NOP, 2016a) leads to an agricultural determination:

1. *Is the substance a mineral or bacterial culture as included in the definition of nonagricultural substance at section 205.2 of the USDA organic regulations?*

No.

2. Is the substance a microorganism (e.g., yeast, bacteria, fungi) or enzyme?

No, although it may contain some enzymatic material.

3. Is the substance a crop or livestock product or derived from crops or livestock?

Yes, RPE is derived from a crop, cereal rye.

4. Has the substance been processed to the extent that its chemical structure has been changed?

Unless a chemical change occurs during the digestion or removal of the outer pollen shell, which is not described in the petition, the answer is no, leading to an agricultural determination.

The extraction of the chemical constituents within the pollen grain's cytoplasm does not transform the substance chemically or physically. The water-soluble fraction consists of the polar components, and the lipid-soluble supercritical carbon dioxide-extracted fraction consists of the nonpolar constituents. Each extraction method, though not thoroughly explained in the petition, exploits the uneven partial charges (or lack thereof) of the constituent molecules through dissolution. Spray-drying of the water-soluble fraction eliminates the solvent and water, through evaporation, leaving the dissolved solids behind. The solvent in the lipid-soluble fraction, carbon dioxide, either off-gasses into the atmosphere following pressure release or condenses back into a liquid for storage or reuse. The dissolved, isolated, and concentrated portions of the source material remain unchanged.

The petition did not specify the identity of the maltodextrin used as a spray-dry carrier in the water-soluble fraction. Although maltodextrin manufacturing processes vary, most involve the acid or enzyme hydrolysis of starches (NOP, 2011). Numerous examples of organic maltodextrin appear in the Organic Integrity Database.

Evaluation of RPE against Guidance NOP 5033-1 *Decision Tree for Classification of Materials as Synthetic or Nonsynthetic* (NOP, 2016b) is discussed below.

1. Is the substance manufactured, produced, or extracted from a natural source?

Yes, the substance is extracted from the pollen of rye.

2b. At the end of the extraction process, does the substance meet all of the criteria described at 4.6 of NOP 5033?

Yes, the material has not been transformed into a different substance via chemical change; the material has not been altered into a form that does not occur in nature; and any synthetic materials used to separate, isolate, or extract the substance have been removed.

2. Has the substance undergone a chemical change so that it is chemically or structurally different than how it naturally occurs in the source material?

No; the chemical constituents within the rye pollen cells remain unchanged. This results in a nonsynthetic determination unless additional process steps are used which were not disclosed in the petition. Unknown processing steps lead to an inconclusive determination.

<u>Evaluation Question #3:</u> If the substance is a synthetic substance, provide a list of nonsynthetic or natural source(s) of the petitioned substance [7 CFR 205.600(b)(1)].

RPE as petitioned is not a synthetic substance unless additional process steps used to digest, remove, or lyse the outer pollen shell initiates a chemical change. This was not described in the petition, so we are unable to make a determination. Based on the manufacturing process submitted by the petitioner and NOP guidance documents NOP 5033-1 & NOP 5033-2, RPE is a nonorganic agricultural ingredient.

<u>Evaluation Question #4:</u> Specify whether the petitioned substance is categorized as generally recognized as safe (GRAS) when used according to FDA's good manufacturing practices [7 CFR 205.600(b)(5)]. If not categorized as GRAS, describe the regulatory status.

Rye, rye pollen, and rye pollen extract do not appear in any FDA GRAS listings for human or animal uses, nor do they appear in the GRAS Notice Inventory. This does not necessarily mean that RPE is not permitted in food.

According to 21 CFR 170.30(c)(1) substances commonly used in food prior to 1958 are permitted without "the quantity or quality of scientific procedures required for a food additive." While rye itself was certainly used as a food staple prior to 1958, it is unclear if an extracted derivative of rye pollen would carry that exemption. The FDA provides a decision tree to help determine if a substance is allowed as a food ingredient, but for those materials that are not listed in the *Substances Added to Food* inventory, the user is instructed to consult with FDA about the regulatory status. We contacted FDA during research for this report and received no reply.

Evaluation Question #5: Describe whether the primary technical function or purpose of the petitioned substance is a preservative. If so, provide a detailed description of its mechanism as a preservative [7 CFR 205.600(b)(4)].

The primary function of RPE is to provide the same nutrient profile as the pollen found in honey, but without the use of bees (Graminex, LLC, 2022). Therefore, the primary function is not as a preservative.

Research related to the application of pollen extracts as an antioxidant in food preservation is scarce. Almeida et al. (2017) compared the lipid oxidation levels over time in refrigerated pork sausage prepared with equivalent inclusion rates of sodium erythorbate and bee pollen extract. The bee pollen extract demonstrated lower rates of lipid oxidation than sodium erythorbate (Almeida et al., 2017). Sodium erythorbate is a synthetic antioxidant related to Vitamin C (USDA, 2023b). The exact phenolic profile of the petitioned product is unknown. However, the Graminex pollen extract profiled by Locatelli et al. (2018) contains a mixture of pollen extracts, one of which is RPE specifically. Applying the phenolic profile outlined by Locatelli et al. (2018) at the inclusion rate described in the petition (Graminex, LLC, 2022) this type of pollen extract product could theoretically provide quercetin and rutin at higher concentrations in the vegan honey substitute than the concentration provided by the bee pollen extract in the sausage evaluated in this study. Consequently, RPE may theoretically have some capacity as a preservative, albeit very limited. However, the application of these phenolic compounds present in pollen extracts for food preservation to additional food products is unknown (Almeida et al., 2017).

Anjos et al. (2019) evaluated the lipid oxidation levels over time in black pudding, another pork product, prepared with 3-sodium ascorbate (E301) and bee pollen extract. The bee pollen demonstrated similar rates of lipid oxidation compared with the ascorbic acid at rates that did not negatively impact consumer evaluation of appearance and flavor.

Sodium erythorbate and 3-sodium ascorbate in these two studies serve as commercial industrial antioxidant controls. The exact mechanisms attributed to the preservation of food by the individual phenolic compounds or any synergistic interactions provided by the complex phenolic profiles present in bee pollen extracts are still unclear (Anjos et al., 2019; Awad et al., 2022).

Evaluation Question #6: Describe whether the petitioned substance will be used primarily to recreate or improve flavors, colors, textures, or nutritive values lost in processing (except when required by law) and how the substance recreates or improves any of these food/feed characteristics [7 CFR 205.600(b)(4)].

RPE is not used to recreate or improve flavors, colors, textures, or nutritive values *specifically lost in processing*. Rather, as petitioned, it is used to recreate nutritive values present in bee pollen, and therefore present in honey, which are not inherently present in honey alternatives (i.e., vegan alternatives). It also does not simulate the texture of honey. Simple sugars, including glucose and fructose, compose the bulk of honey. These sugars impart the textural attributes apparent to the consumer, including adhesion and granularity (Machado De-Melo et al., 2018; Moumeh et al., 2020). The carbon dioxide extraction that produces the lipid-soluble RPE leaves no sugars in the final product to recreate this texture (Li et al., 2021; X. Xu et al., 2011). The water extraction that produces the water-soluble RPE also leaves no sugars in the final product.

RPE may improve the flavor of a vegan sweetener alternative to honey, but the flavor profile may not recreate the full flavor profile of bee pollen. The water-soluble fraction of RPE has acidic notes and a hay-like odor, as does the oil-soluble fraction, which also has some bitter notes (Graminex, LLC, 2022). These are sensory attributes also present in bee honey via the bee pollen (Marcazzan et al., 2018). However, some of the volatile flavor compounds contributing to the flavor of honey are derived from floral nectar or honeydew (sugar-rich insect secretion) (Kaškonienė et al., 2008; Machado et al., 2020). Wind-pollinated plants, such as cereal rye, do not make nectar (Saunders, 2018). Aphids and other insects feeding on trees are a common source of honeydew consumed by honeybees, although other insect-plant associations can be sources, too (Gounari et al., 2023; Özbay et al., 2022; Shantal Rodríguez Flores et al., 2015). Additional factors that contribute to the flavor profile of honey include honeybee secretions, thermal processing, and storage conditions (Kaškonienė et al., 2008). Volatile compounds that influence flavor are known to persist in water- and oil-soluble extracts derived from botanical materials (Capuzzo et al., 2013; Galindo-Cuspinera et al., 2002).

Similar to the effect on flavor profile, pollen is also known to contribute to the hue of the honey (Anupama et al., 2003; Sousa et al., 2016). The water-soluble fraction of RPE is beige and the oil-soluble fraction is dark green-brown to almost black (Graminex, LLC, 2022). These hues are not dissimilar from those present in bee honey (Marcazzan et al., 2018).

<u>Evaluation Question #7:</u> Describe any effect or potential effect on the nutritional quality of the food or feed when the petitioned substance is used [7 CFR 205.600(b)(3)].

The primary function of RPE stated in the petition is to mimic the nutrient profile of the pollen component found in honey in a vegan sweetener (Graminex, LLC, 2022). Pollen is known to contain varying levels of the following nutrients (Machado De-Melo et al., 2018):

- carbohydrates
- proteins
- enzymes
- amino acids
- vitamins
- minerals
- phenolic compounds

The nutrient profile that bee pollen provides to honey can vary by botanical origin (source), and may be further influenced by seasonal and regional variation (Chantarudee et al., 2012).

Plant extracts derived from pollen contain phenolic compounds (see *Composition of the Substance*), proteins, and amino acids (Li et al., 2021). The phenolic compounds of both honey (Cheung et al., 2019) and pollen extracts (Chiavaroli et al., 2022; Locatelli et al., 2018) are associated with some health-promoting properties. Locatelli et al. (2018) is the only study we found that describes the phenolic compounds in a mixture of pollen extracts that contains RPE specifically.

Cane nectar and date nectar are the primary ingredients in the vegan honey substitutes produced by the collaborator named in the petition (*The Single Origin Food Co. - Amber Vegan Un-Honey, 8oz*, 2023; *The Single Origin Food Co. – Blonde Vegan Un-Honey, 8oz*, 2023; *The Single Origin Food Co. - Copper Vegan Un-Honey, 8oz*, 2023). Refined cane sugar does not contain the bioactive compounds (e.g., vitamins, minerals, and phenolic compounds) found in honey, although non-centrifugal cane sugars may retain some phenolic compounds after processing. Date nectar does retain several vitamins and minerals through processing (Castro-Muñoz et al., 2022).

<u>Evaluation Question #8:</u> List any reported residues of heavy metals or other contaminants in excess of FDA tolerances that are present or have been reported in the petitioned substance [7 CFR 205.600(b)(5)].

There are no established FDA limits for heavy metals or other contaminants for RPE. The FDA has not established limits for heavy metals or microbial contaminants in finished foods, including sweeteners and table syrups (U.S. FDA, 2023c). Bakers yeast extract may be the most analogous material to RPE as a processed extract, and the FDA has set the following heavy metal limits for that material (U.S. FDA, 2023b):

- 0.4 ppm arsenic
- 0.13 ppm cadmium

- 0.2 ppm lead
- 0.05 ppm mercury
- 0.09 ppm selenium
- 10 ppm zinc

Pollen can accumulate heavy metals from environmental pollution (Kalbande et al., 2008; Vasilevskaya, 2022). Kalbande et al. (2008) examined levels for environmental contaminants in both unexposed and exposed pollen from three plant species. Researchers detected lead in unexposed pollen with a reported range of 0-0.3 ppm, but it was detected in exposed pollen with an increased range of 0.6-11.7 ppm (Kalbande et al., 2008). The FDA's Action Levels for Poisonous or Deleterious Substances in Human Food and Animal Feed does set limits for lead, but these restrictions apply only to cooking utensils and dishware (U.S. FDA, 2023a).

Aflatoxin has been detected in bee pollen, with reported levels at upwards of 26 ppb mean concentration (Végh et al., 2021). The FDA's Action Levels for Poisonous or Deleterious Substances in Human Food and Animal Feed sets limits for aflatoxins in human foods at 20 ppb (U.S. FDA, 2023a). Additionally, the FDA sets the following limits for bakers yeast extract (U.S. FDA, 2023b):

- Less than 10,000 organisms/gram by aerobic plate count
- Less than 10 yeasts and molds/gram
- Negative for *Salmonella*, *E. coli*, coagulase positive *Staphylococci*, *Clostridium perfringens*, *Clostridium botulinum*, or any other recognized microbial pathogen or any harmful microbial toxin

<u>Evaluation Question #9:</u> Discuss and summarize findings on whether the manufacture and use of the petitioned substance may be harmful to the environment or biodiversity [7 U.S.C. 6517(c)(1)(A)(i) and 7 U.S.C. 6517(c)(2)(A)(i)].

Impact of rye crop production

Climate change and ecotoxicity are two impact categories where intensive agriculture has demonstrably negative effects compared to organic agriculture across a variety of crop types (Boschiero et al., 2023). The studies cited evaluate farming systems based on life cycle assessments (LCAs). These assessments often exclude important variables such as biodiversity, soil organic carbon, and overall soil quality (Boschiero et al., 2023). Nonorganic rye is the source of the RPE in this petition (Graminex, LLC, 2022). The petitioner grows 400-600 acres of nonorganic rye, which is planted in fall and harvested in the spring (Graminex, LLC, 2022). RPEs are niche products, to be used in other niche products (vegan honey substitutes). As such, it is unlikely that farmers would need to grow large amounts of rye to support pollen extract products.

Impact studies on rye are limited. Kim et al. (2022) evaluated the carbon and water dynamics of perennial rye and annual rye. The perennial rye demonstrated greater atmospheric carbon uptake compared to the annual rye. The terrestrial water balance was similar between both rye crops. The manufacturing process described in the petition suggests the use of annual rye (Graminex, LLC, 2022). Noya et al. (2018) found in a study of conventional cereal crops for livestock feed that between barley, rye, and sorghum, rye had the lowest environmental impact. Additionally, rye is a common cover crop often planted to control soil erosion. However, it can become a weed, particularly when planted before winter wheat (Casey, 2012; White et al., 2006).

Some evidence suggests that conventional agriculture can negatively affect the size and diversity of insect pollinator populations. This is attributed to the use of pesticides, the reduction of nesting sites available, and the reduction of foraging opportunities (Bretagnolle & Gaba, 2015). On the use of pesticides, rye is generally more resistant to pests than other cereal grains. However, it is listed as a Class C noxious weed in Washington state that may warrant control measures (Casey, 2012).

We found no studies directly implicating rye as a source of food or nesting sites for insect pollinator populations. Rye is wind-pollinated, and these plants do not typically rely on insect pollination. However, there is evidence that insect pollinators will collect pollen from wind-pollinated plants. These plants may provide essential food resources in some regions and/or seasons. Rice, corn, and sorghum are wind-pollinated cereal grains known to be visited by bees and syrphid flies for pollen (Harris-Shultz et al., 2022; Saunders, 2018).

Impact of rye pollen extraction

Extraction of the water-soluble and lipid-soluble fractions of RPE are carried out via water extraction and supercritical CO_2 extraction, respectively (Graminex, LLC, 2022). Both methods offer non-toxic alternatives with less environmental concerns compared to conventional organic solvent extraction methods (L. Wang & Weller, 2006).

Impact of RPE use in food

The constituents of the RPE as naturally occurring substances found in plants are also naturally occurring in the environment. We did not find literature that indicated any negative impact on the environment or biodiversity resulting from the use of RPE in food.

<u>Evaluation Question #10:</u> Describe and summarize any reported effects upon human health from use of the petitioned substance [7 U.S.C. 6517(c)(1)(A)(i), 7 U.S.C. 6517(c)(2)(A)(i)), and 7 U.S.C. 6518(m)(4)].

We found no documented evidence of specific health risks or benefits related to the consumption of RPE as an ingredient in processed foods. Discussion of the reported effects on human health of the related materials bee pollen, raw rye pollen, and pollen extracts as therapeutic agents are included below for broader consideration of strictly theoretical health implications related to consumption of the petitioned material.

Acute and chronic toxicity

We did not find literature that indicated there is any clear toxicity risk associated directly with RPE.

Several studies identified varying levels of lead, cadmium, and arsenic in bee pollen. Two of these studies found honey with lead levels that exceeded the maximum limit (100 µg/kg of honey, wet weight) set by the European Commission Regulation No 1881/2006 (amended 09.08.2021). Concentrations of lead, cadmium, and arsenic in bee pollen vary with pollution levels, climate, season, and weather conditions (Nowak & Nowak, 2023).

Allergen risk

We did not find literature that indicated any clear allergen risk associated directly with RPE.

Pollen allergens associated with the grasses family (Poaceae) are some of the leading causes of hay fever worldwide. Research shows sensitization levels to raw rye pollen ranging from 27.7-90.0% among studied cohorts (Damialas & Konstantinou, 2011). A patent describing the manufacture of a cytoplasmic pollen extract notes that the source material is the inner part of the pollen seed devoid of its envelope. The envelope is typically a source of allergens (Morra, 2019). A patent describing another manufacturing process involves digestion of the pollen by a mold (*Mucor hiemalis*) and also claims to reduce allergens in the pollen extract product (Gosta, 1967).

Health benefits

Researchers have demonstrated that pollen extracts are effective for the treatment of prostatitis in controlled human clinical trials (Cai et al., 2017; Muraca et al., 2022; Yasumoto et al., 1995). Side effects reported in clinical trials were generally uncommon and mild if they did occur (Antonelli et al., 2019; Cai et al., 2017; Yasumoto et al., 1995). The biological mechanisms by which pollen extract achieves this clinical impact are still not entirely clear. There is some evidence that it has anti-inflammatory qualities. Cai et al. (2017) demonstrated that pollen extract and vitamins reduced the levels of pro-inflammatory cytokine IL-8 in patients with chronic prostatitis and chronic pelvic pain syndrome.

Locatelli et al. (2018) and Chiavaroli et al. (2022) found a significant presence of phenolic compounds in a pollen extract nutraceutical containing a mixture of standardized pollen of rye grass (*Secale cereale L.*), corn (*Zea mays L.*), and timothy (*Phleum pratense L.*). In an in vitro experiment, Chiavaroli et al. (2022)

demonstrated that pollen extracts caused an anti-inflammatory and antioxidant response in human prostate cancer and ovarian cancer cells. Furthermore, an in silico[4] study suggests phenolic compounds may have a role in the biological mechanisms of action, particularly catechin and chlorogenic acid (Chiavaroli et al., 2022). There is also limited evidence that chlorogenic acid (another component of pollen extracts) may be involved in the body's regulation of glucose and blood pressure (Lin et al., 2016).

Some researchers suggest that pollen extract may significantly reduce menopausal symptoms with low side effects (Genazzani et al., 2020; Sailer & Regidor, 2019).

There is some evidence that honey, like pollen extracts, demonstrates potential as a source of bioactive compounds with anti-inflammatory and antioxidant effects (Bogdanov et al., 2008; Castro-Muñoz et al., 2022). In a review article, Bogdanov et al. (2008) note that consuming honey for the purported health benefits provided by the bioactive compounds involved substantial daily intake doses of 50 to 80 g. RPE is petitioned for use in a vegan sweetener that may otherwise lack the full complexity of bioactive compounds typically attributed to honey (Castro-Muñoz et al., 2022). However, we found no research in the literature that directly compares the therapeutic effects and effective doses of honey and pollen extracts (RPE or otherwise) in vitro or in vivo.

Evaluation Question #11: Describe any alternative practices that would make the use of the petitioned substance unnecessary [7 U.S.C. 6518(m)(6)].

The petitioner of RPE intends to use the substance as an added ingredient to organic honey vegan alternatives, to mimic the 'pollen aspect' of honey (Graminex, LLC, 2022). An alternative practice is to continue to omit the ingredient in these honey alternatives. Another alternative practice is to obtain organic certification for this agricultural ingredient. The petitioner noted that breeding stock with high pollen-producing potential is commercially unavailable from an organic source (Graminex, LLC, 2022). Since 7 CFR 205.204(a) allows nonorganic, untreated seed to be used for the production of an organic crop when an organically produced variety is not commercially available, the lack of available breeder stock should not pose a barrier to organic certification.

Evaluation Question #12: Describe all natural (non-synthetic) substances or products which may be used in place of a petitioned substance [7 U.S.C. 6517(c)(1)(A)(ii)]. Provide a list of allowed substances that may be used in place of the petitioned substance [7 U.S.C. 6518(m)(6)].

The beneficial components of RPE that mimic those found in bee pollen are available from nonagricultural sources, though not necessarily in the same quantity or combination as in RPE. For example, nonsynthetic, nonagricultural ingredients permitted by 7 CFR 205.605(a) of the National List are sources for some of same nutrients:

- calcium carbonate
- calcium chloride
- calcium sulfate
- magnesium chloride
- magnesium sulfate
- potassium chloride
- potassium iodide

Synthetic nutrient vitamins and minerals are also permitted at 7 CFR 205.605(b)(20) in accordance with 21 CFR 104.20 for foods labeled "organic" or "made with organic (specified ingredients or food groups)" and could also be used in place of RPE for some of the same nutritional function it provides to vegan syrups.

However, the quantity of these nutrients in RPE as opposed to mined mineral or synthetic nutrient sources is not comparable, and we found no information to suggest that formulators of vegan honey alternatives include such additives in their products. Additionally, it is difficult to compare impacts from the potential

[4] Experimentation via computer simulation

use of RPE to the potential use of mineral or synthetic nutrients in vegan syrups since sources and production practices for these different ingredients vary widely.

Non-GMO enzymes and yeast are also permitted as ingredients in organic products and contain some of the same beneficial compounds as RPE, including amino acids, vitamins, minerals, phenolic compounds (Vieira et al., 2016) and superoxide dismutase (SOD) enzymes. Vieira et al. (2016) analyzed the nutritional and phenolic content of lyophilized spent brewers yeast and found it to be rich in essential amino acids, trace elements, and macronutrients including B complex vitamins that provide antioxidant properties. Chiavaroli et al. (2022) reported the phenolic compounds in pollen extracts with therapeutic activity to be catechin, chlorogenic acid, gentisic acid, and 3-hydroxytyrosol. Brewers yeast also contains the phenolic compounds catechin and chlorogenic acid, along with numerous others, some of which are also found in RPE: rutin, isoquercetin, and cinnamic acid. Like RPE, yeast is a functional ingredient, though its nutrient and phenolic compound profiles do not match exactly. We found no reported use of yeast extracts or enzymes as functional ingredients in vegan syrups.

Biologically active compounds such as those found in RPE may also come from a variety of different sources. Xu et al. (2017) note that natural antioxidants occur widely in food and medicinal plants. Agricultural alternatives are discussed in *Evaluation Question 13*.

<u>Evaluation Information #13:</u> Provide a list of organic agricultural products that could be alternatives for the petitioned substance [7 CFR 205.600(b)(1)].

At the time of this report there are over 1500 sources of organic rye listed in the NOP organic integrity database (OID) (USDA, 2023a). However, according to the petitioner, the specific breeder stock of rye used to produce the pollen from which RPE is extracted is not commercially available in organic form (Graminex, LLC, 2022), possibly due to the prevalence of rye breeding for grain production rather than pollen production (Geiger & Miedaner, 2009). However, organic regulations at 7 CFR 205.204(a) allow nonorganic, untreated seed to be used for the production of an organic crop when an organically produced variety is not commercially available. Certification of the petitioner's rye farm and processing facility may be possible, even if the specific seed used is not available in organic form.

The OID (2023a) does list sources of certified organic chamomile pollen[5], dill pollen[6], fennel pollen[7], and pine pollen[8]. Like RPE, chamomile pollen contains a significant amount of polyphenols capable of inhibiting biochemical pathways that lead to inflammation of the prostate (Locatelli et al., 2018). Fennel (specifically its seeds and oil) also contains bioactive compounds (not necessarily the same as those found in RPE): trans-anethole, p-coumaric acid and rosmarinic acid, and has a variety of therapeutic uses (Uusitalo et al., 2016). We did not find information on the content of nutritional or bioactive compounds in fennel or dill pollen specifically.

One can harvest and extract pollen from any number of different certified organic plants. Timothy grass and corn, for example, are both available from organic sources (USDA, 2023a). The petitioner combines these pollens with RPE in some of their products (Locatelli et al., 2018). Žilic et al. (2014) reported on the chemical composition and biological activity of corn pollen, and identified many of the same nutritional components and polyphenols found in RPE, such as flavonoid glycosides, quercetin, and rutin, as well as isorhamnetin. The authors note similar functions to RPE including antioxidant activity, anti-inflammatory, anti-carcinogenic and cardio-protective effects, and benefits to endothelial functioning (Žilić et al., 2014). Bujang et al. (2021) also found these beneficial nutritive and bioactive functions in corn pollen.

Bujang et al. (2021) compared corn pollen to numerous other floral and bee pollens in terms of moisture content, fiber, mineral content, and total phenolic content. They found, for example, that alfalfa, date palm,

[5] Suppliers: Al Ahram Herbs Company (Egypt), All Ingredients Plus, Inc. (U.S.), Herbs World Co. (Egypt), High Quality Organics, Inc. (U.S.), Kraeuter Mix Lanka (Pvt) Ltd. (Sri Lanka), Nabil Mohamed Morsi Company (Egypt), Organic Green for food industry (Egypt), Pure Ground Ingredients (U.S.), Starwest Botanicals, LLC (U.S.),

[6] Supplier: Central Valley Plant and Seed dba Kandarian Organic Farms (U.S.)

[7] Suppliers: Central Valley Plant and Seed dba Kandarian Organic Farms (U.S.), Pollen Collection & Sales, Inc. dba Pollen Ranch (U.S)

[8] Suppliers: Chocolita ("Pine Pollen Lemon") (U.S.), QINGDAO HEAD TECHNOLOGY CO., LTD (China)

saffron, rapeseed, and sunflower pollens all contained similar levels of macro and micronutrients, but that corn pollen was higher in certain nutrients like magnesium. Date, olive, palm, and saffron pollen all possess levels of fiber and moisture content similar with one another; separately, two species of corn pollen, two species of rose pollen, and one bee pollen (*M. interrupta*) are all similar in their fiber and moisture content. The last group with similar moisture content and fiber consisted of alfalfa pollen, oil palm pollen, rapeseed pollen, sunflower pollen and *A. mellifera* bee pollen (Bujang et al., 2021).

There are also numerous sources of certified organic bee pollen. Bee pollen contains additional components not found in floral pollens, resulting from the action of the bees' salivary enzymes on sugars in the collected pollen. Bee pollen is also likely higher in lipid content than plant-collected pollen; researchers have documented bees visiting plants with higher lipid-containing pollen more frequently than those with lower lipid content (El Ghouizi et al., 2023). Bees also increase lactic ferments in hive storage nectar that is used by the bees in pollen collection, which can result in bee pollen containing lactic acid bacteria that can function as a probiotic in human food (El Ghouizi et al., 2023). However, the basis for the petition is to have an alternative to honey which contains the beneficial compounds of pollen from a vegan source. Isolated bee pollen does not meet this requirement.

Non-bee floral pollen differs to some extent from the ingredient it intends to replace, bee pollen. Given that, the other, already-available certified organic pollens or pollens from certified organic crop flowers appear to be potentially viable alternatives.

Other potential alternatives to the inclusion of RPE in vegan honey substitutes are extracts of bioactive compounds from plants and plant parts other than pollen. Xu et al. (2017) reported on extraction techniques to obtain beneficial polyphenolic compounds from a wide range of foods and medicinal plants such as fruits, vegetables, mushrooms, cereals, spices, flowers, and medicinal herbs. The potential of any of these extracts to serve as an alternative to RPE in vegan syrups is unknown and likely dependent on numerous factors. We did not find any information to suggest that formulators use botanical extracts as functional ingredients in vegan syrups.

Report Authorship

The following individuals were involved in research, data collection, writing, editing, and/or final approval of this report:

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