Bergamot Bitter Orange Powder

Handling/Processing

Identification of Petitioned Substance

Chemical Names:
Citrus aurantium L. subspp. Bergamia

Other Names:
Bergamot *Citrus aurantium* powder, Bigarade, Citrus vulgaris, Hesperidin, Limon, Sour Orange, naringin, neroli, Seville orange, Shangjao Zhiqiao (Chinese), Kijitsu (Japanese), Naranja Amarga (Spanish), Narandam (Tamil); Petitgrain extract; Neroli absolute.

Trade Names:
Citrox BC Concentrate, Citrox Sanitizer 14T, Citrox Detergent 14X, Citrox Processing Aid 14W

CAS Numbers:
72968-50-4 (bitter orange powder)
520-26-3 (hesperidin)
10236-47-2 (naringin)
13241-33-3 (neohesperiden)

Other Codes:
EINACS: 277-143-2

Characterization of Petitioned Substance

Composition of the Substance:

The substance is composed of the natural powdered flavonoids from bitter oranges. The chemical constituents of bergamot and bitter oranges are complex and include a number of essential oils, flavonoids and biogenic amines. Among the substances isolated from bitter orange include camphen, cresol, hesperidin, isocriocin, limonene, linalool, naringin, naringenin, neodiosmin, neohesperidin, nerol, p-octopamine, α-pinene, poncirin, p-synephrine, N-methyltyramine, tyramine, hordenine (Heidary et al., 2003; NTP, 2004; McCarley, 2011). The peel and zest consist largely of glucosides. The fruit contains approximately 1% protein. The remaining essential oils consist of various terpenes and phenolic structures.

Properties of the Substance:

Table 1.
Physical, Chemical and Nutritional Properties of Bergamot Bitter Orange Powder

Physical or Chemical Property:	Value:
Physical State	Solid
Appearance	Light brown hydroscopic powder having a characteristic flavor and bitter taste.
Odor	Odorless
Solubility	Soluble in water, glycerol / water (80:20), propylene glycol and aqueous alkali. Partially soluble in ethanol.
Relative Density	0.85-0.95 g/cc
pH	2.5-5.5 (1% w/v)
Calories	37-66/100g
Protein	0.6-1.0 g/100g
Fat	trace-0.1 g/100g

Physical or Chemical Property:	Value:
Carbohydrates	9.7-15.2 g/100g
Fiber	0.4 g/100g
Ash	0.5 g/100g
Calcium	18-50 mg/100g
Iron	0.2 mg/100g
Phosphorus	12 mg/100g
Vitamin A	290 µg/100g or 200 I.U. /100g
Thiamine	100 µg/100g
Riboflavin	40 µg/100g
Niacin	0.3 mg/100g
Ascorbic Acid	45-90 mg/100g

Sources: Exquim, 2001; Morton, 1987 (bitter orange dry weight)

Specific Uses of the Substance:

The substance is petitioned for use as a processing aid, as a water pH modifier in fruit and vegetable wash, and meat carcass rinse. The petition also describes use as a disinfectant to be used in direct contact with organic food, including as a fruit and vegetable wash and for application to meat carcasses (McCarley, 2011).

Other uses include as a flavoring agent for food and beverages and as a component in herbal and flavored black teas. Bergamot is an essential ingredient in Earl Grey tea. Bitter orange has been historically used as a fragrance in perfumes and as a component in bitter tonics (Walter, 1916). Extracts of the dried fruit and peel have long been used in Ayurvedic, Chinese, Japanese and Western herbal medicine (Bentley, 1887; Tierra, 1988; Huang, 1999; NTP, 2004). Specifically, bitter orange has been used as a substitute for ephedra (also known as Ma Huang and Mormon Tea) (NTP, 2004). As such, it is prescribed by naturopathic practitioners for respiratory function, as a stimulant and for weight loss (Tierra, 1988). Neroli extracted from bitter orange is also listed as a hypnotic, an aphrodisiac and a euphoric (Lis-Balchin, 2006). Additionally, bitter orange powder can be used to dye cotton, linen and other natural fibers (Kaneko, 2004).

Approved Legal Uses of the Substance:

Bergamot bitter orange (bergamot orange / *Citrus aurantium* L. subsp. Bergamia Wright et Arn) is generally recognized as safe by the US FDA (21 CFR 182.20) and is used as an ingredient in food as a natural extractive. The petitioned substance is considered an antimicrobial biopesticide by the US EPA (Jones, 2002). It is not currently registered with EPA as a pesticide, and does not have a tolerance or tolerance exemption for use as a biopesticide at this time. (US EPA, 2012).

Action of the Substance:

Flavonoids are polyphenolic substances that are well documented to carry out a number of biological activities (Benavente-García et al., 1997; Duthie and Crozier, 2000; Mandalari et al., 2007). The specific antimicrobial properties of the flavonoids are not specifically known. Flavonoids function as direct antioxidants and free radical scavengers (Cavia-Saiz, 2010; Mandalari et al., 2007). Flavonoids also have the capacity to modulate enzymatic activities and inhibit cell proliferation (Duthie and Crozier, 2000).

Early research in using various citrus-based disinfectants yielded inconsistent results. Continued research with the various constituents indicates that some combinations of substances are more effective than

others. Efficacy can be increased by formulating with certain adjuvants. Some combinations to increase efficacy may involve synthetic chemical modification of the phenolic structures (Céliz, et al., 2011).

Combinations of the Substance:

The petitioned use involves the formulation of products using proprietary formula that has not been fully disclosed to the reviewers (McCarley, 2011). The National Organic Standards Board (NOSB) originally reviewed the formulated product and noted that several of the substances contained in the formulation were already on the National List and may not need to be petitioned. However, the NOSB recommended that Bitter Orange be petitioned (NOSB, 2005). This Technical Evaluation Report does not address all of the ingredients in commercial products used as antimicrobial pesticides for direct application to food.

Common combinations of the substance with ingredients include various teas and flavorings. Various sources refer to combinations used for fragrance (Walter, 1916), as herbal remedies (Tierra, 1988) and for various culinary flavorings.

Status

Historic Use:

Bergamot and bitter orange have been used as ingredients in herbal and flavored black teas and as a part of preparations for herbal remedies, and as a flavoring agent. The juice of bitter orange has been traditionally used in Africa as a topical antiseptic on ulcers and lesions (Morton, 1987).

OFPA, USDA Final Rule:

Bergamot bitter orange powder does not appear specifically in OFPA (7 USC 6501 *et seq.*) or the USDA Final Rule (7 CFR 205). As an agricultural product, bergamot bitter orange powder is subject to the requirement of 7 CFR 205.105(d) that prohibits the use of '[n]onorganic agricultural substances used in or on processed products, except at otherwise provided in §206.606 . . .'

International

Canada - Canadian General Standards Board –
Bergamot and bitter orange do not explicitly appear in the Permitted Substances List. In particular, bergamot and bitter orange are not contained in either §7.3, "Food-Grade Cleaners, Disinfectants and Sanitizers That Are Allowed Without a Mandatory Removal Event" or §7.4, "Cleaners, Disinfectants and Sanitizers Allowed on Food-Contact Surfaces including Equipment Provided That Substances Are Removed From Food-Contact Surfaces Prior to Organic Production" (CGSB, 2009).

CODEX Alimentarius Commission - ftp://ftp.fao.org/docrep/fao/005/Y2772e/Y2772e.pdf
The Codex guidelines are silent on the use of antimicrobial substances in post-harvest handling. However, the Guidelines state that the "[u]se of pesticides not listed in Annex 2 for post-harvest or quarantine purposes should not be permitted on products prepared in accordance with these guidelines and would cause organically produced foods to lose their organic status." Annex 2 is not an exhaustive list. Member states may permit substances based on the criteria in §5.1. Bitter orange powder does not explicitly appear on Annex 2, but "Natural Plant Preparations, Excluding Tobacco" does, so one could infer it to be permitted.

European Economic Community (EEC) Council Regulation, EC No. 834/2007 and 889/2008
The petition claims the substance to be approved under EC 834/2007 (McCarley, 2011). The European

regulation is silent on disinfectants used in direct contact with organic food and that has been broadly interpreted as allowance of all disinfectants approved for direct use on food.

Bergamot and bitter orange used as ingredients in processed food products are subject to Article 8 of EC 834/2007, which requires "the production of organic food from organic agricultural ingredients, except where an ingredient is not available on the market in organic form . . ." Article 28 of EC No. 889/2008 requires ingredients of non-organic origin to be on Annex IX when used in an organic processed product. Neither bitter orange nor bergamot appears on Annex IX.

International Federation of Organic Agriculture Movements (IFOAM) –The *IFOAM Basic Standards* §6.6.2 permits the use of water and disinfectants on Appendix 4, Table 2 to be used in direct contact with food. The list of disinfectants is indicative, not exhaustive, and standard setting bodies are required to evaluate additional substances according to the Criteria found in Appendix 1.

Agricultural ingredients are required to be from organic sources according to §6.2.1, with a derogation for standard setting bodies to permit the use of non-organic ingredients where organic ingredients are not available in sufficient quality or quantity (IFOAM, 2005). A certificate from Bio-Gro New Zealand is included within the petition; however, it refers only to products used in crop production and does not indicate whether intervening events are required.

Japanese Agricultural Standard (JAS) for Organic Production –
There is no specific mention of bergamot or bitter orange in The Japanese Agricultural Standard governing the processing of organic food products. JAS requires organic products not be 'polluted' by disinfectants, but does not specifically limit which disinfectants can be applied directly to organic food. JAS also requires ingredients in organic food to be of organic agricultural origin, but allows for exceptions provided that those ingredients are not produced using 'recombinant DNA technology' or 'ionizing radiation' (JMAFF, 2000).

Evaluation Questions for Substances to be used in Organic Handling

Evaluation Question #1: 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)).

Bitter orange can be prepared by a number of different methods. The simplest is to dry and crush the unripe fruit by mechanical means. Bitter orange powder can be prepared by drying the peels to under 30% moisture—in the optimal range of 15-25% moisture—mechanically pulverizing them (Kaneko, 2004).

The petition provides information regarding the steps used to extract the flavonoids and receive the target concentration (McCarley, 2011). The process described is mostly mechanical, using physical methods such as freezing, thawing, drying, slicing and filtering using membranes.

Intact, immature non-organic Bergamot bitter oranges are frozen to disrupt cell tissue, then thawed, sliced and comminuted with water. Water soluble components are extracted multiple times; filtered (macro) and the liquid extract ultra-filtered using synthetic polymer membranes. After filtering to remove pulp and other insoluble material, the water extract is passed through ion exchange resin which retains the citrus bioflavonoids. Included in the process is the use of various adsorbents, such as Amberlite XAD7HP or Dowex (McCarley, 2011). Their manufacturer considers these to be ion exchange resins (Dow, 2011). The ultra-filtered extract containing the bioflavonoids is then pumped through adsorbent matrix in a packed column as a means of purification. That is, the bioflavonoids are attached to the column, non-covalently, presumably by hydrophobic/hydrophilic and dipole interactions.

The citrus bioflavonoids are eluted from the ion exchange resin by aqueous ethyl alcohol (70%). The solution is evaporated to recover most of the alcohol and then spray dried to produce the dry, alcohol-free powder (McCarley, 2011). The solution is then evaporated under vacuum to reduce the boiling point.

The concentrated bioflavonoid solution is then pumped into a spray drier. Spray drying involves pumping the concentrated solution through an atomizer revolving at up to 5,000 RPM where droplets usually smaller than 10 microns hit hot dry air (180°C) in a counter current mode, so that the droplets, when impacted in the hot dry air are instantly dried with particles falling to the bottom of the conical spray drying chamber. There should be no covalent bonds broken as a function of both evaporation and spray drying. The solution is then spray dried, standardized and sent for further processing into a formulated product (McCarley, 2011).

The NOSB specifically asked about the claim made that the substance was 'solvent-free' (NOSB, 2005). The petitioner responded with information as to how the ethanol is evaporated through spray-drying with analyses used to support their claim (McCarley, 2011). Another method to produce solvent-free bitter orange extract is to use supercritical carbon dioxide (CO_2) (Mukhopadhyay, 2000). Carbon dioxide is listed on 205.605(b), while non-organic ethanol is not on the National List for handling or processing.

Evaluation Question #2: Is the substance synthetic? 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)).

Bergamot bitter orange powder is considered a natural extractive (21 CFR 182.20). As such, it is commonly accepted as a non-synthetic agricultural product.

Evaluation Question #3: Provide a list of non-synthetic or natural source(s) of the petitioned substance (7 CFR § 205.600 (b) (1)).

Both bergamot and bitter orange are non-synthetic or natural agricultural products. The main source is the Seville region of Spain, but the crop is widely cultivated in other places with Mediterranean and subtropical climates, including California, Florida, Hawaii, Brazil, China and India. Hesperidin, naringin and other polyphenolic flavonoids are found in other citrus species as well, such as sweet orange (*Citrus sinensis*), lemon (*C. limon*), lime (*C. aurantifolia*), tangerine (*C. reticulate deliciosa*) and citron (*C. medica*).

Table 2 lists sources of organic bitter orange reported on the USDA National Organic Program's website:

Table 2
Sources of USDA Certified Organic Bergamot and Bitter Orange

Operator	Location	Accredited Certification Agent
A. Fakhry & Co.	Egypt	Ceres
Aliaga	Paraguay	BCS
Aliquima	Paraguay	Ceres
Amigo y Arditi	Paraguay	Ceres
Amrita Aromatherapy	Iowa, USA	Oregon Tilth
Arylessence	Georgia, USA	Oregon Tilth
Astier-Demerest	France	EcoCert
B2 Organic	New Jersey, USA	Tilth
Best SRL	Italy	Certisys
Carmien Tea	South Africa	EcoCert
Citroflor	Italy	Suolo E Salute
Difusions Organique	France	EcoCert
Ditta Pizzi Ezio e Giovanni	Italy	Certisys

Operator	Location	Accredited Certification Agent
El Taller, Asociación de Promoción y Desarrollo	Peru	IMO
Fytosan	France	EcoCert
Golgemma	France	EcoCert
Joaquin Ramon Rubio	Seville, Spain	CAAE
Juan Luis Ramon Rubio	Seville, Spain	CAAE
KIC Chemicals	New York, USA	Oregon Tilth
Laboratoire Iris	France	EcoCert
Lapacho Imex	Paraguay	BCS
Lavandas de las Sierras	Argentina	Argencert
L'Herbier du Diois	France	EcoCert
Midwest Herb	Missouri, USA	OneCert
Pizzi Ezio Azienda	Italy	Certisys
Plantes Aromatiques Du Diois	France	EcoCert
Sirius	France	EcoCert
Dierberger Óleos Essênciais	Brazil	IBD
Spinelli, Maria	Italy	Certisys
Superior Natural Foods	Minnesota, USA	Organic Certifiers

Source: NOP 2012.

Evaluation Question #4: 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. What is the technical function of the substance?

Bergamot bitter orange powder is generally recognized as safe (GRAS) when used according to FDA's good manufacturing practices (GMPs). In addition, according to the FDA, bitter orange is GRAS for human consumption (21 CFR 182.20) and as an ingredient in animal feed (21 CFR 582.20). The petitioned technical function of the substance is as an antimicrobial (McCarley, 2011), but the substance has a number of other technical effects, mostly as a flavoring (Walter, 1916), an antioxidant, a free radical scavenger, an anti-inflammatory and a repellant or toxin to certain insects (Benaventa-Garcia, et al., 1997).

Evaluation Question #5: Describe whether the primary function/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 in the petition is as an antimicrobial (McCarley, 2011). As an antioxidant, free radical scavenger and antimicrobial, the polyphenols contained in bergamot and bitter orange can retard spoilage (Benavente-Garcia et al., 1997).

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)).

The substance is petitioned for use as a disinfectant (McCarley, 2011). Bitter orange may be used as a flavoring and a coloring agent. The bitterness of bitter orange may impart specific flavors desired.

Evaluation Question #7: 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)).

Bergamot bitter orange powder contains various nutrient vitamins and minerals, in particular: ascorbic acid (vitamin C), vitamins A, B_1 (thiamine), B_2 (riboflavin), B_3 (niacin), calcium, iron and phosphorous (Morton, 1987). Citrus components are documented to have a beneficial synergistic effect on the metabolism of various nutrients (LSRO, 1982; Rouseff, 1994; Economos and Clay, 1999). There is no indication from the data that the substance would have a negative effect on the nutritional quality of food when used as a disinfectant. The concentrated constituents of the petitioned application, hesperidin and naringin, are reported to have low bioavailability (Ameer, et al., 1996).

Evaluation Question #8: 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)).

Non-organic oranges may have pesticide residues that are commonly used in conventional production and are not allowed in organic production. The USDA's *Pesticide Data Program* reported that between 80% and 86% of all orange samples had detectable levels of pesticides over the years 1993-2003 (Punzi et al., 2005). The peel will have more residues than the flesh. For the most recent year where the PDP had data, 2009, 683 out of 744 samples collected tested positive for at least one pesticide (Fry, 2011). EPA Tolerances and FDA Action Levels for oranges (all types) are contained in Table 3.

Table 3
EPA Tolerances or FDA Action Levels for Pesticides in Oranges

Pesticide	Tolerance (PPM)
Aldrin	0.02
Crotoxyphos	1.00
Dieldrin	0.02
Dimethoate including its oxygen analog	2.00
Formetanate hydrochloride	1.50
Malathion	8.00
1-Naphthaleneacetic acid	0.10
O-Phenylphenol and its sodium salt	10.00
Propargite	10.00
Simazine	0.25

Sources: 40 CFR 180; FDA, 2000.

Because the petitioned use is for food contact and not as a food ingredient, exposure would be less than what would be expected if the substance was directly ingested.

The manufacturer of the polymeric absorbents state that these processing aids contain by-products of their manufacturing process and that it is the user's responsibility to see that these by-products are removed (Rohm and Haas, 2006). Ion exchange resins used in the extraction process are subject to degradation (Dow, 1997). The petition did not explain how these resins are removed from the final product.
The Food Chemicals Codex does not have a monograph on 'Bergamot Bitter Orange Powder.' There are monographs for bergamot oil, bitter orange oil, and petitgrain oil (Food Chemicals Codex, 2009).

Evaluation Question #9: 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)).

As a citrus fruit, bitter orange can be intensively produced. While the petition claims that sources are organically produced, but not certified, no verification of this claim is offered in the petition (McCarley, 2011). Bitter orange produced is subject to infestation by fruit flies of the Tephritidae and Lonchaeidae

families (Ladaniya, 2008). Mediterranean fruit fly (*Ceratitis capitata*) is endemic to Spain and other places in the Mediterranean region, where most of the petitioned fruit is produced. Various experiments showed that the Mediterranean fruit fly preferred citrus— including bitter orange—to other foliage when mating (Katsoyannos, et al., 1999). Pesticides commonly used on citrus to control the Mediterranean fruit fly in citrus include various organophosphates, synthetic pyrethroids and neonicotinoids (Raga and Soto, 2011). Citrus peels extracts are insecticidal against mosquito larvae (Mwaiko, 1992).

The manufacturing process described in the petition does not include any volatile aromatic solvents or other processing aids that would cause air or water pollution.

Evaluation Question #10: 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)).

There is an extensive amount of literature on the effects of citrus and its various components on human health (LSRO, 1982; Rouseff, 1994; Economos and Clay, 1999, among others). The human health effects of flavonoids and related polyphenolic structures include their ability to scavenge free radicals, module enzymatic activity, and inhibit cellular proliferation, as well as the antimicrobial activity claimed in the petition (Bravo, 1998). In addition to antimicrobial activity, flavonoids derived from citrus fruits also have properties that are linked to cancer prevention, cardiovascular health and reduction of inflammation (Tripoli, et al., 2006). Reported human health impacts of flavonoids are preponderantly positive, but there are some safety concerns and conflicting results, particularly when the components are eaten as supplements in isolation from the plant matrix in which they are naturally stored (Ross and Kasum, 2002).

Many of the studies regarding citrus flavonoid health effects—including those cited in the petition—were for citrus fruits other than the ones petitioned. The specific properties of bergamot bitter orange, particularly the alkaloids that account for its distinctive bitterness, may have effects not otherwise accounted for in the literature. These alkaloids have attracted attention for their technical and functional effects. Claimed health benefits from the use of bergamot and bitter orange components as dietary supplements, such as weight loss, have yielded mixed preliminary results (Bent et al., 2004; Haaz et al., 2006).

The FDA is concerned that some of the characteristics that bitter orange shares with ephedra will result in similar reported adverse health impacts (NTP, 2004). No action has been taken by the FDA at this time. Bitter orange and grapefruit share their bioflavonoid profiles; both contain naringin. Naringin is the component of grapefruit that alters drug-metabolizing enzymes in the human intestine, leading to sub-potency or life-threatening super-potency of various drugs (Stump, et al., 2006; Li et al., 2007).

Bitter orange has been identified to have 568 constituents with active phytochemical properties (Duke, 2011). While most of the effects listed are mild or beneficial, the substance is listed as allergenic and as an irritant. The database also notes that bitter orange contains small amounts of the toxic substance formic acid (2011). The petition is for food contact only and not as an ingredient. Most of the above uses as dietary supplements or in tea involve significantly higher ingestions than when the disinfectant is used according to label instructions. Misuse by direct consumption would result in a higher ingestion of bergamot bitter orange powder than consumption as a minor ingredient in food.

The petitioned substance has been screened on human subjects as an oral hygiene product and may be effective as a broad-spectrum antimicrobial mouthwash (Hooper, et al., 2011).

Evaluation Information #11: Provide a list of organic agricultural products that could be alternatives for the petitioned substance (7 CFR § 205.600 (b)(1)).

The substance is an agricultural product. The manufacturing process may necessarily involve processing aids and food contact substances that are not permitted in organic processing or handling. The flavonoids found in bitter orange are found in other citrus fruits, albeit in different proportions. Hesperidin is the predominant flavonoid found in lemons and sweet oranges (Merck, 2006). Other agricultural products identified as effective as disinfectants include anise, camphor, clove, eucalyptus, lavender, lemongrass, peppermint, sandalwood and thyme (McCue and Smialowicz, 1995). At the time of this report, there were no known commercial formulations made from organic agricultural products that could be used as an antimicrobial in direct food contact.

The alternatives currently used in organic processing and handling that the petition proposes to replace are not organic agricultural products. Chlorine products on 7 CFR 205.605(b)—calcium hypochlorite, sodium hypochlorite and chlorine dioxide—are the main alternatives that the petition seeks to replace. A comparison of bergamot bitter orange powder with chlorine products using the OFPA criteria is beyond the scope of this report.

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