ANSES Opinion
Request No 2017-SA-0215

The Director General

Maisons-Alfort, 23 May 2018

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on three cases of allergy to food supplements containing pollen or hive products

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with the necessary information concerning these risks as well as the requisite expertise and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are made public.
This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 23 May 2018. shall prevail.

1. BACKGROUND AND PURPOSE OF THE REQUEST

Under the nutrivigilance scheme it set up in 2009, ANSES has received three reports of severe adverse effects (Level 3 severity on a scale of 4) likely or very likely to be associated with the consumption of food supplements containing pollen or hive products. These reports involved the following pollen or hive products[1]: Gelée Royale 1000 mg® chewable tablets taken with Vitalité 4G Dynamisant® sticks manufactured by Forté Pharma (2016-328), Propolia® propolis gums manufactured by Apimab (2015-086), and Sérélys®[2] tablets from Sérélyspharma (2012-153).

Given the severity of the adverse effects described and the commonality of these three reports, ANSES, in accordance with the quality procedure relating to nutrivigilance, felt it necessary to bring them to the attention of the general public and health professionals, with a view to improving protection of consumer health.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French standard NF X 50-110 “Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)”.

ANSES entrusted the expert appraisal to two external rapporteurs and to the Working Group (WG) on "Nutrivigilance". This opinion was discussed on 16 January 2018 and adopted on 30 January

[1] Hive products are the products that bees collect (pollen, nectar, propolis) or produce (honey, royal jelly).

[2] The product involved in the report has now become a range of several products. In the text of the opinion below, the name "Sérélys®" will refer to the product as declared in 2012, containing pollen extract and vitamin E.

2018 by the "Nutrivigilance" WG, and then presented to the CES on "Human Nutrition" on 14 March 2018, the date on which the document was validated.

3. ANALYSIS AND CONCLUSIONS OF THE WG AND THE CES

3.1. Nutrivigilance case 2016-328 (Gelée Royale 1000 mg® chewable tablets and Vitalité 4G Dynamisant®)

3.1.1. Product composition

According to publicly available information, one Gelée Royale 1000 mg® chewable tablet contains 333 mg of lyophilised royal jelly equivalent to 1000 mg of fresh royal jelly. One stick of Vitalité 4G Dynamisant® product contains the following main ingredients: 290 mg of acerola titrated in vitamin C, 150 mg of ginseng, 85 mg of guarana, 80 mg of lyophilised royal jelly equivalent to 240 mg of fresh royal jelly, 50 mg of caffeine and 30 mg of ginger.

3.1.2. Case description

This involved a 29-year-old woman with a pollen allergy who was not undergoing any treatment. On 13 October 2016, as part of a taste test for a laboratory, she took one chewable tablet of Gelée Royale 1000 mg® food supplement and one stick of Vitalité 4G Dynamisant® food supplement. Fifteen minutes later, her eyes became red, she started sneezing and experienced a runny nose, difficulty breathing, bronchospasm, cough and flushing.

She went to the hospital emergency department where she received an infusion of corticosteroids and an adrenaline spray. An antihistamine (Aerius®) and a corticosteroid (prednisolone) were prescribed when she left hospital.

She then consulted her allergist who confirmed from specific tests an allergy to certain pollens including from grasses and mugwort. She was advised to avoid all products or foods containing honey, royal jelly or other hive products.

Since then, she has not experienced any new crisis.

This clinical picture equates to Level 3 severity on the nutrivigilance scale[3].

3.1.3. Causality

The food supplements' causality in the occurrence of allergic effects was analysed by applying the method defined in the ANSES opinion of 11 May 2011 on the development of a method for determining causality in reports of adverse reactions in nutrivigilance (ANSES 2011).

3.1.3.1. Intrinsic score

The chronological score refers to the time taken for the adverse effect to appear, its progression and its recurrence when the products are reintroduced. In this case, the 15-minute onset time for the effect was found to be compatible. Since the effect abated after discontinuation of the products

[3] The scale of severity in nutrivigilance goes from Level 1 (low severity) to Level 4 (death).

and after emergency treatment, the progression was described as "suggestive". The food supplements were not reintroduced. Based on this information, the chronological score is C3[4].

The semiological score is determined after establishing a differential diagnosis for the observed effect. In this case, pollen allergy is a risk factor for royal jelly allergy (Dutau 2009). The semiological score is therefore S2[5].

The intrinsic score, which results from the combination of the chronological score and the semiological score, is therefore I3, meaning that the food supplements are likely responsible for the occurrence of the allergic effect[6].

3.1.3.2. Extrinsic score

3.1.3.2.1. Bibliographical score

The bibliographical score reflects the scientific knowledge available at the time of the search for the adverse effects reported for a product and/or its components. The following search was only concerned with adverse effects of an allergic nature.

- **Royal jelly**

In 1997, a survey was conducted among employees of a university hospital in Hong Kong in order to study consumption of and hypersensitivity to royal jelly. Of the 1472 employees who responded to the questionnaire, 461 subjects (31.3%) admitted having taken royal jelly in the past, including nine subjects (0.6%) who reported a total of 13 royal jelly adverse effects. The effects described were urticaria, eczema, conjunctivitis, rhinitis and dyspnea. The asthma of one asthmatic subject was exacerbated following the consumption of royal jelly. In addition, two subjects reported having had several episodes of allergic reaction within two hours of taking royal jelly (Leung *et al.* 1997).

Several cases of anaphylactic shock, anaphylaxis, asthma or bronchospasm following ingestion of royal jelly have been reported in other articles. They are summarised in Table 1 below.

The bibliographical score for this component is B3[7].

[4] The chronological score ranges from C0 to C4.
[5] The semiological score ranges from S0 to S3.
[6] The intrinsic score ranges from I0 (excluded) to I4 (very likely).
[7] The bibliographical score ranges from B0 to B3. A B3 score corresponds to a notable effect.

Table 1: Cases reported in the literature of anaphylactic shock, anaphylaxis, asthma or bronchospasm caused by royal jelly

Authors	Sex, age	Medical history	Product, quantity	Timeframe between ingestion and occurrence of symptoms	Clinical signs	Allergy tests	Comments
Roger *et al.* (1995)	F, 15 years	Atopic predisposition	Royal jelly, unknown quantity	15 minutes	Localised angioedema, generalised urticaria, dysphonia and bronchospasm	Prick-to-prick[8] test positive for 1/10 dilution of royal jelly	
Peacock, Murray, and Turton (1995)	F, 31 years	Mild asthma	Royal jelly, two capsules	40 minutes	Severe respiratory difficulties, cyanosis, drowsiness, asthenia, bradypnea and tachycardia	None	Six weeks later, she again experienced breathing difficulties 40 minutes after ingesting royal jelly
Leung *et al.* (1995)	F, 26 years	Moderate asthma	Royal jelly and ginseng, one capsule	30 minutes	Asthma attack	Skin-prick test[9] positive for royal jelly Oral challenge test positive (severe asthma 90 minutes later)	Royal jelly first consumed two days previously
	F, 33 years	Asthma	Fresh royal jelly, half a teaspoon	20 minutes	Severe asthma attack, rhinoconjunctivitis and angioedema	Skin-prick test positive for royal jelly	Royal jelly already consumed once two years previously

[8] The "prick-to-prick" is a skin-prick test used for fresh food. The fresh food is pricked first and then the skin is pricked with the same needle.
[9] The skin-prick test is an epidermal micropuncture performed by a lancet or needle.

Authors	Sex, age	Medical history	Product, quantity	Timeframe between ingestion and occurrence of symptoms	Clinical signs	Allergy tests	Comments
	M, 66 years	Asthma	Royal jelly, unknown quantity	30 minutes	Asthma, anaphylaxis and respiratory arrest	Skin-prick test positive for royal jelly	Royal jelly already consumed previously
	F, 19 years	Asthma	Royal jelly, unknown quantity	20 minutes	Asthma, rhinitis and upper airway obstruction	Skin-prick test positive for royal jelly	Royal jelly consumed for the first time
	F, 23 years	Asthma	Royal jelly, unknown quantity	60 minutes	Acute wheezing	Skin-prick test positive for royal jelly	Royal jelly consumed for the first time
	F, 30 years	Asthma	Royal jelly, unknown quantity	20 minutes	Acute asthma	Skin-prick test positive for royal jelly	Royal jelly first consumed two days previously
	F, 43 years	Asthma	Royal jelly, unknown quantity	5 minutes	Dyspnea, wheezing, angioedema and hypotension	Skin-prick test positive for royal jelly	Royal jelly consumed for the first time
Harwood *et al.* (1996)	M, 22 years	Asthma	Royal jelly, one tablet	20 minutes	Severe asthma attack, urticaria and conjunctivitis	None	No aetiology other than royal jelly was identified for this case
	M, 23 years	Asthma	Royal jelly, one tablet	2 hours	Dyspnea then cardiac arrest Subcutaneous emphysema, pneumomediastinum and extensive urticaria within 24 hours	None	Royal jelly tablet taken for the first time in the previous three days. Two hours later, slight wheezing occurred

Authors	Sex, age	Medical history	Product, quantity	Timeframe between ingestion and occurrence of symptoms	Clinical signs	Allergy tests	Comments
Laporte *et al.* (1996)	F, 17 years	Atopic asthma	Royal jelly, unknown quantity	30 minutes	Bronchospasm, urticaria	None	The last asthma attack (unknown cause) was five years previously
	M, 17 years	Atopic asthma	Royal jelly, ginseng, tocopherol, unknown quantity	2 hours	Bronchospasm, pruritus	None	The last asthma attack (unknown cause) was nine years previously
	F, 19 years	No history of asthma	Royal jelly, unknown quantity	30 minutes	Bronchospasm, swelling of the eyelids	None	Co-trimoxazole taken 12 hours before the bronchospasm occurred
Anzfa (2002)	F, 11 years	Allergy to dust mites, cats, horses and plantain pollen	Royal jelly, one 10 mL vial	20 minutes	Diarrhoea, severe bronchospasm, breathing difficulties, vomiting, cardiac arrest, death	None	Shock occurred after the fourth exposure to royal jelly. Asthma attack during the penultimate exposure
	M, 31 years	Mild asthma	Royal jelly, unknown quantity	Unknown time	Severe asthma attack, cardiorespiratory arrest, death	None	Doubts about the responsibility of royal jelly
	F, 23 years	Mild asthma	Royal jelly, one 2000 mg capsule	Unknown time	Dyspnea progressing to severe asthma attack, cardiac arrest, death	Negative tryptase assay	Causality of royal jelly deemed possible

Authors	Sex, age	Medical history	Product, quantity	Timeframe between ingestion and occurrence of symptoms	Clinical signs	Allergy tests	Comments
Takahama and Shimazu (2006)	M, 33 years	Not specified	Royal jelly, Pabron Ace®, Bishin Club Seatome® and Bishin Club Vitamin C&E®, unknown quantity	A few hours	Dizziness, numbness of fingers, generalised itching, dyspnea, wheezing, loss of consciousness, generalised erythema, frontal oedema	Skin-prick test positive for royal jelly only	Royal jelly already taken several times in the past, without any reaction
Testi *et al.* (2007)	M, 28 years	Severe asthma	Cefonicid, dosage unknown Royal jelly, unknown quantity	15 minutes	Dyspnea, wheezing, coughing, tightness of the chest after the 4th injection of Cefonicid The next day, severe dyspnea and loss of consciousness 15 minutes after the 5th injection of Cefonicid	Skin-prick test positive for royal jelly Skin-prick test and intradermal test negative for Cefonicid	During the diagnostic procedure, it was discovered that the patient was using royal jelly after each injection
Katayama, Aoki, and Kawana (2008)	F, 26 years	Bronchial asthma, rhinitis, allergic conjunctivitis, atopic dermatitis	Pure royal jelly beverage, unknown quantity	15 minutes	Anaphylaxis, generalised erythema, pruritus, swelling of the eyelids, wheezing, hypoxemia and loss of consciousness	Skin-prick test positive for pure royal jelly beverage	Royal jelly already taken previously, but first time this beverage was consumed

Authors	Sex, age	Medical history	Product, quantity	Timeframe between ingestion and occurrence of symptoms	Clinical signs	Allergy tests	Comments
Suzuki *et al.* (2011)	M, 18 years	Not specified	Crushed royal jelly packaged in a pouch, consumed during a meal, unknown quantity	60 minutes	Wheezing, dyspnea, facial oedema, impaired consciousness during jogging	Skin-prick test positive for royal jelly Oral challenge test positive	Sport alone did not induce asthma or anaphylaxis
Mizutani *et al.* (2011)	F, 26 years	Bronchial asthma	Royal jelly, one tablet	30 minutes	Dyspnea, severe facial oedema and erythema	Skin-prick tests positive for tablet powder and royal jelly powder	Royal jelly beverage taken previously, but first time tablet form was consumed
Vila, Bartolome, and Moreno (2013)	F, 11 years	Intermittent sneezing, nasal pruritus and rhinorrhoea	Beverage containing royal jelly and fructose, unknown quantity	2 hours	Dysphonia, cough, wheezing and angioedema of the eyelids	Skin-prick tests positive for royal jelly and house dust mites Oral challenge test positive for royal jelly	First time this beverage was consumed Experiments conducted show that *Dermatophagoides pteronyssinus* proteins and royal jelly proteins have common allergenic epitopes. Prior sensitisation to dust mites possible

Authors	Sex, age	Medical history	Product, quantity	Timeframe between ingestion and occurrence of symptoms	Clinical signs	Allergy tests	Comments
Fantini *et al.* (2014)	F, 7 years	None	Royal jelly, unknown quantity	10 minutes	Swelling of the tongue and lips, itching of the palate	Skin-prick test positive for royal jelly IgE antibodies specific to other allergens found	A cross-reaction mechanism with other allergens is possible
RAV (2015)	F, 39 years	Seasonal rhinitis in adolescence and rhinoconjunctivitis to animal epithelia	Royal jelly, one gram	Immediate	Anaphylactic shock	Skin-prick test positive for the incriminated royal jelly	First case involving royal jelly declared to the Allergo-Vigilance Network (RAV)

- **Acerola**

Only one case of anaphylactic reaction (urticaria, itching, dyspnea, and tachycardia) has been reported, in a 37-year-old man, five minutes after consuming apple juice supplemented with acerola. He had experienced seasonal hay fever for thirteen years and suffered since childhood from severe contact urticaria induced by latex products. He also had a history of allergies to avocado, celery, walnuts/hazelnuts and curry. Skin tests with acerola pulp and acerola-containing apple juice produced immediate reactions. An oral challenge test was performed with apple juice and acerola pulp diluted in water, as well as with apple juice without acerola. The results were negative for the apple juice, while the acerola pulp caused itching and swelling of the lips after five minutes. According to the authors, prohevein (Hev b 6.01) was the major allergenic protein involved in the development of a cross-reaction between latex and acerola in this patient (Raulf-Heimsoth *et al.* 2002).

The bibliographical score for this component is B2[10].

- **Ginseng**

Two cases of allergy after ingestion of ginseng have been reported.

The first described the case of a 20-year-old man with no prior history of allergies, who presented with generalised urticarial rash and breathing difficulties three minutes after ingesting a sip of ginseng syrup. On arrival at the emergency department, he had hypotension, and discrete angioedema on his extremities, trunk, neck, face, feet and hands. The symptoms disappeared after an injection of dexamethasone. No allergy tests were conducted due to the patient's refusal (Wiwanitkit and Taungjaruwinai 2004).

The second case involved a 44-year-old man with a history of rhinitis who developed rhinorrhoea, nasal congestion, breathing difficulties and abdominal pain 10 minutes after ingesting fresh Korean ginseng. The results of the skin-prick test were positive for ginseng extract and fresh ginseng. An oral challenge test was performed with 50 g of fresh ginseng. The patient immediately developed facial flushing, cough and difficulty breathing with wheezing and abdominal pain (Lee *et al.* 2012).

Moreover, two cases of occupational asthma occurring after inhalation of ginseng dust have also been described in the literature (Lee *et al.* 2006, Kim *et al.* 2008)

The bibliographical score for this component is B2.

- **Caffeine**

Several cases of anaphylaxis, urticaria or hypersensitivity to coffee or caffeine have been reported in the literature. They are summarised in Table 2 below.

The bibliographical score for this component is B2.

[10] A B2 score corresponds to an effect reported in the scientific literature by well conducted studies.

Table 2: Cases reported in the literature of anaphylaxis, urticaria or hypersensitivity to caffeine

Authors	Sex, age	Medical history	Product, quantity	Timeframe between ingestion and occurrence of symptoms	Clinical signs	Allergy tests	Comments
Pola *et al.* (1988)	F, 48 years	None	Coffee, tea or chocolate, unknown quantity	15 minutes	Generalised urticaria	Skin-prick test and intradermal test positive for caffeine extract. Oral challenge test positive in 15 minutes for 100 mg caffeine	Symptoms appeared 15 minutes after each intake of caffeine-containing substances
Quirce Gancedo *et al.* (1991)	M, 53 years	Atopic predisposition, aspirin idiosyncrasy	Coffee, tea, cola or chocolate beverage, unknown quantity	20 minutes	Itching, erythema and wheals on the face, neck and upper trunk	Oral challenge test positive for 25 mg caffeine	Symptoms following ingestion of coffee, tea, cola beverage or chocolate had existed for 15 years
Caballero *et al.* (1993)	M, 10 years	None	Coffee, 1 cup (first consumption)	5 minutes	Generalised urticaria	Skin-prick test positive for 10 mg/mL anhydrous caffeine Oral challenge test positive in 30 minutes for 160 mg caffeine citrate	After this initial reaction, he experienced a few less severe episodes of urticaria, some of which were associated with the ingestion of cola-based beverages
Moneret-Vautrin *et al.* (1993)	M, 65 years	Urticaria in 1988 Anaphylactic shock in 1989	Coffee and beta-blocking eye-drops containing timolol, unknown quantity	30 minutes	Collapse with brief loss of consciousness, generalised erythema, bradycardia then cardiac arrest	Skin-prick test positive for ground coffee, caffeine, prepared ground coffee and gum arabic	The authors retained the diagnosis of dual anaphylaxis to coffee and gum arabic, aggravated by the use of beta-blocking eye drops

Authors	Sex, age	Medical history	Product, quantity	Timeframe between ingestion and occurrence of symptoms	Clinical signs	Allergy tests	Comments
Daroca *et al.* (1996)	F, 53 years	None	Coffee, tea or cola beverage, unknown quantity	2 hours	Chills, high fever, myalgia and headache	Skin-prick test negative for 50 mg/mL of caffeine Oral challenge test positive in 1 hour for 60 mg of caffeine	Symptoms following ingestion of coffee, tea or cola beverage had existed since childhood A cross-reaction with theophylline was observed
Hinrichs *et al.* (2002)	F, 69 years	Generalised urticaria on six occasions after drinking a cup of coffee	Thomapyrin®: 250 mg of aspirin, 200 mg of paracetamol and 50 mg of caffeine	Not indicated	Generalised urticaria	Oral challenge test negative for 1 to 100 mg of caffeine Oral challenge test positive for 150 mg caffeine Skin-prick test positive for caffeine	The results of the skin-prick test and the oral challenge tests show that the induction of urticaria by caffeine is dose-dependent
Fernández-Nieto, Sastre, and Quirce (2002)	F, 19 years	Atopic predisposition	Coca-Cola®, unknown quantity	Not indicated	Recurrent episodes of acute generalised urticaria for eight years	Oral challenge test positive in 10 minutes for 630 mL of classic Coca-Cola® Skin-prick test negative for caffeine Intradermal test positive for 1 mg/mL of caffeine Oral challenge test positive for 50 mg caffeine	The patient noticed that the greater the amount of Coca-Cola® ingested, the greater the rash

Authors	Sex, age	Medical history	Product, quantity	Timeframe between ingestion and occurrence of symptoms	Clinical signs	Allergy tests	Comments
Infante *et al.* (2003)	M, 9 years	Atopic predisposition	Coffee, 1 cup	30 minutes	Pruritus on the soles of the feet and palms, generalised urticaria, cough, wheezing and shortness of breath	Skin-prick test positive for 10 mg/mL of caffeine IgE antibodies specific to caffeine and caffeinated Coca-Cola® detected	These symptoms reappeared after the consumption of at least two cola beverages
Tognetti, Murdaca, and Fimiani (2014)	F, 24 years	Six episodes of urticaria between 2006 and 2011	Coffee or cappuccino, 1 cup	Not indicated	Oedema of glottis, diarrhoea and loss of consciousness	Oral challenge test positive for 50 mg caffeine Reactions after 1 to 2 minutes	An oral challenge test for 50 mg of theophylline was positive after nine hours
Sugiyama *et al.* (2015)	F, 27 years	None	Candy containing 42 mg of caffeine	Not indicated	Throat pruritus, dyspnea, generalised urticaria, angioedema, anaphylaxis	Skin-prick test positive for 5 and 50 mg/mL of caffeine	Five days after anaphylaxis, she developed throat pruritus after drinking green tea and then after ingesting coffee jelly

- **Guarana**

To date, no cases of allergy specific to guarana have been published. However, guarana seed contains caffeine (3.6-5.8%). People who are hypersensitive to caffeine may therefore also be hypersensitive to guarana.

The bibliographical score for this component is B0[11].

- **Ginger**

To date, no cases published in the literature have shown the existence of allergies caused by ginger ingestion.

On the other hand, one case of allergic rhinitis and one case of asthma following exposure to ginger dust in an occupational setting have been published (Malo and L'Archevêque 2011, Schmidt, Dahl, and Sherson 2015). Ginger can also cause contact dermatitis (Schöll and Jensen-Jarolim 2004, Chen and Bahna 2011)

The bibliographical score for this component is therefore B1[12].

3.1.3.2.2. Other cases recorded in the nutrivigilance database

To date, no other cases of allergy to the Gelée Royale 1000 mg® or Vitalité 4G Dynamisant® food supplements have been reported.

Table 3 below lists cases of allergy and hypersensitivity that may be associated with the consumption of other food supplements containing royal jelly, caffeine, acerola, ginseng, ginger and/or guarana.

Table 3: Other cases of allergy or hypersensitivity involving food supplements containing royal jelly, caffeine, acerola, ginseng, ginger and/or guarana

Identification number	Food supplement	Composition	Effect(s)	Sex, age	Causality	Severity	Comments
2013-205	Alvityl Petit Boost®	Honey, **royal jelly**, iron, zinc, vitamins A, B1, B2, B3, B5, B6, C and D	Generalised urticaria	M, 9 years	Possible	Level 2	Child with allergic asthma (dust mites and grasses)
2013-206	Alvityl Petit Boost®	Honey, **royal jelly**, iron, zinc, vitamins A, B1, B2, B3, B5, B6, C and D	Generalised urticaria	M, 13 years	Possible	Level 2	Child with dust mite allergy Combined with Ventilastin®

[11] A B0 score corresponds to an effect that has never been reported.

[12] A B1 score corresponds to an effect reported in very few scientific publications.

Identification number	Food supplement	Composition	Effect(s)	Sex, age	Causality	Severity	Comments
2014-037	Pediakid Mal des Transports®	Agave syrup, acacia fibres, mint extract, orange, lemon, **ginger**, sage, milk thistle	Urticaria, pruritus	F, 9 years	Possible	Level 2	No allergy tests conducted
2014-364	Force G Power Max®	**Ginseng, ginger, guarana**, taurine, arginine, **acerola** and vitamin C	Urticaria	M, 32 years	Possible	Level 1	Onset of urticaria two hours after taking the food supplement No allergy tests conducted Combined with potassium permanganate, Dermoval®, Betadine® solution and Amycor®
2017-183	Respiratoire Sirop Gorge®	Honey, fig, lemon, propolis, **acerola**, marshmallow and echinacea root, pine bud, *Verbascum*, essential oil of eucalyptus, lemon, rosemary and peppermint	Anaphylaxis	M, 4 years	Likely	Level 3	Immediate reaction Misuse, because product not recommended for children under seven years of age Allergy tests not available

3.2. Nutrivigilance case 2015-086 (Propolia® propolis gums)

3.2.1. Product composition

According to publicly available information, six propolis gums contain 935 mg of honey and 330 mg of propolis extract.

3.2.2.Case description

This involved a 65-year-old woman with a history of allergy to *Ficus*. In February 2012, she first took a propolis gum from the Propolia® brand. This initial intake led to swelling of the tongue and mouth ulcers after two to three days. The symptoms disappeared within five days of administration of antibiotics and corticosteroids.

One month later, she again took a propolis gum. Three hours later, this caused significant swelling of the lips and discomfort, then pharyngeal dyspnea. Taking antihistamines (Aerius®) led to an improvement within a few hours. These symptoms then progressed as with the first time to mouth ulcers and desquamation of the tongue.

The allergy assessment did not show any reaction to this propolis gum in the skin-prick test.

This clinical picture equates to Level 3 severity on the nutrivigilance scale[13].

3.2.3.Causality

The food supplement's causality in the occurrence of allergic effects was analysed by applying the method defined in the ANSES opinion of 11 May 2011 on the development of a method for determining causality in reports of adverse reactions in nutrivigilance (ANSES 2011).

3.2.3.1. Intrinsic score

The chronological score refers to the time taken for the adverse effect to appear, its progression and its recurrence when the products are reintroduced. In this case, the two- to three-day onset time for the effect was found to be compatible. Since the effect abated after discontinuation of the products and after emergency treatment, the progression was described as "suggestive". In addition, the product was reintroduced after the adverse effect had abated. This reintroduction is classified as positive since the adverse effect reappeared. Based on this information, the chronological score is C4[14].

The semiological score is determined after establishing a differential diagnosis for the observed effect. In this case, the consumer had an allergic predisposition. The semiological score is therefore S2[15].

The intrinsic score, which results from the combination of the chronological score and the semiological score, is therefore I4, meaning that the food supplement was very likely responsible for the occurrence of the allergy effect[16].

3.2.3.2. Extrinsic score

3.2.3.2.1. Bibliographical score

The bibliographical score reflects the scientific knowledge available at the time of the search for the adverse effects reported for a product and/or its components. The following search was only concerned with adverse effects of an allergic nature.

[13] The scale of severity in nutrivigilance goes from Level 1 (low severity) to Level 4 (death).
[14] The chronological score ranges from C0 to C4.
[15] The semiological score ranges from S0 to S3.
[16] The intrinsic score ranges from I0 (excluded) to I4 (very likely).

- **Honey**

A few cases of allergic effects following ingestion of honey have been reported in the literature (Table 4). It appears that honey often contains other substances derived from bees or associated with their activities, such as proteins from their salivary glands or pollen (Bousquet, Campos, and Michel 1984, Birnbaum *et al.* 1989, Helbling *et al.* 1992, Florido-Lopez *et al.* 1995, Kiistala *et al.* 1995, Bauer *et al.* 1996, Lombardi *et al.* 1998, Dutau 2009). It is these substances that are responsible for the allergic effects.

The bibliographical score for this component is B2[17].

[17] The bibliographical score ranges from B0 to B3. A B2 score corresponds to an effect reported in the scientific literature by well conducted studies.

Table 4: Cases reported in the literature of allergies caused by the ingestion of honey

Author(s)	Sex, age	Medical history	Product, quantity	Timeframe between ingestion and occurrence of symptoms	Clinical signs	Allergy tests
Bousquet, Campos, and Michel (1984)	F, 42 years	Allergy to Compositeae pollens	Honey, 1 teaspoon	15 minutes	Angioedema of the lips, pulse at 195 beats per minute, blood pressure at 110/70 mmHg	High specific IgE antibodies against Compositeae pollens
Birnbaum *et al.* (1989)	M, 50 years	Food allergy to celery	Sunflower honey, unknown quantity	A few minutes	Anaphylactic reaction	Skin-prick test positive for Compositeae pollens, celery and sunflower honey, high specific IgE antibodies against sunflower honey
Kalyoncu (1997)	F, 40 years	Rhinoconjunctivitis in autumn and spring for nine years	Honey, unknown quantity	Not indicated	Anaphylactic reactions after ingestion of honey and cake with honey	Skin-prick test positive for *Artemisia* and *Olea* pollens
	M, 47 years	Rhinoconjunctivitis in spring, food allergies to hazelnuts and apples	Honey, unknown quantity	Not indicated	Pruritus, swelling of the lips and throat, gastrointestinal disorders	Skin-prick test positive for birch

Author(s)	Sex, age	Medical history	Product, quantity	Timeframe between ingestion and occurrence of symptoms	Clinical signs	Allergy tests
Fuiano *et al.* (2006)	F, 19 years	Allergic to Compositeae pollens, rhinoconjunctivitis for seven years	Honey and bread, unknown quantity	10 minutes	Angioedema of the lips and tongue, runny nose, cough, dyspnea, loss of consciousness	Skin-prick test positive for Compositeae pollens, prick-to-prick test positive for certain honeys ("Millefiori", from bees foraging on Compositeae, sunflower, lime and eucalyptus)
Tuncel *et al.* (2011)	M, 14 months	None	Honey, 5 teaspoons	5 minutes	Swelling of the lips, urticaria, angioedema, cough and wheezing	Prick-to-prick test positive for the ingested honey
Neziri-Ahmetaj, Neziri, and Fatime (2013)	F, 52 years	None	Honey, unknown quantity	10 minutes	Urticaria, angioedema, cough and wheezing	Skin-prick test positive for birch and chamomile
RAV (2015)	F, 31 years	Pollinosis	Honey, 2 teaspoons	20 minutes	Anaphylactic shock	Skin-prick test positive for plantain, mugwort and grasses Honey-specific IgE antibodies

Author(s)	Sex, age	Medical history	Product, quantity	Timeframe between ingestion and occurrence of symptoms	Clinical signs	Allergy tests
Aguiar *et al.* (2017)	F, 36 years	None	Honey, unknown quantity	20 minutes	Generalised urticaria	Prick-to-prick test positive for the ingested honey and for eucalyptus, sunflower, orange blossom, strawberry tree, lavender, heather and rosemary honeys

- **Propolis**

Although few cases of allergies occurring after ingestion of propolis have been described in the literature (Table 5), dermal application of products containing propolis is known to cause contact dermatitis (Wanscher 1976, Tennstedt and Lachapelle 1977, Rudzki and Grzywa 1983, Cirasino, Pisati, and Fasani 1987, Schuler and Frosch 1988, Silvani *et al.* 1997, Downs and Sansom 1998, Bae *et al.* 2004, Elgezua *et al.* 2006, Jacob, Chimento, and Castanedo-Tardan 2008, Münstedt and Kalder 2009, Rodríguez-Jiménez *et al.* 2010, Basista and Filipek 2012, Jagtman, De Groot, and Bakker 2016).

The bibliographical score for this component is B2.

Table 5: Cases reported in the literature of allergies caused by the ingestion of propolis

Author(s)	Sex, age	Medical history	Product, quantity	Timeframe between ingestion and occurrence of symptoms	Clinical signs	Allergy tests
Young (1987)	M, 55 years	Not specified	Tablets and toothpaste containing propolis	Not indicated	Stomatitis, pain in the throat	Patch test positive for Balsam of Peru and propolis
Callejo *et al.* (2001)	M, 10 years	Five minutes after being stung by a bee, urticaria, angioedema, hypotension and faecal and urinary incontinence	The child helps his beekeeper father in handling hive products	Not indicated	Angioedema	Prick-to-prick test positive for propolis High specific IgE antibodies against bee venom and propolis
Cho, Lee, and Cho (2011)	F, 36 years	None	Propolis solution produced by a beekeeper, unknown quantity	Not indicated	Pruritic, multiple erythematous papules, patches and edema of the face, neck, arms, abdomen and thighs	Patch test positive for propolis

3.2.3.2.2. Other cases recorded in the nutrivigilance database

To date, no other cases of allergy to the food supplement Propolia® propolis gums have been reported.

Table 6 below lists cases of allergy or hypersensitivity that may be associated with the consumption of other food supplements containing honey and propolis, in particular.

Table 6: Other cases of allergy or hypersensitivity involving food supplements containing honey and propolis

Identification number	Food supplement	Composition	Effect(s)	Sex, age	Causality	Severity	Comments
2011-080	Tonic C+®	Camu-camu, vitamin C, **propolis**	Skin rash, pruritus	M, 62 years	Possible	Level 1	No allergy tests performed
2013-166	Oropolis® honey and lemon lozenges	**Propolis**	Stomatitis	F, 65 years	Very likely	Level 2	Symptoms appeared 30 minutes after taking the food supplement Patch tests positive for propolis and the ingested product
2013-205	Alvityl Petit Boost®	**Honey**, royal jelly, iron, zinc, vitamins A, B1, B2, B3, B5, B6, C and D	Generalised urticaria	M, 9 years	Possible	Level 2	Child with allergic asthma (dust mites and grasses)
2013-206	Alvityl Petit Boost®	**Honey**, royal jelly, iron, zinc, vitamins A, B1, B2, B3, B5, B6, C and D	Generalised urticaria	M, 13 years	Possible	Level 2	Child with dust mite allergy Combined with Ventilastin®
2016-247	Aagaard Propolis – Grande A®	**Propolis**	Skin rash	M, 51 years	Possible	Level 2	No allergy tests performed Patient undergoing chemotherapy

Identification number	Food supplement	Composition	Effect(s)	Sex, age	Causality	Severity	Comments
2017-183	Respiratoire Sirop Gorge®	**Honey**, fig, lemon, **propolis**, acerola, marshmallow and echinacea root, pine bud, *Verbascum*, essential oil of eucalyptus, lemon, rosemary and peppermint	Anaphylaxis	M, 4 years	Likely	Level 3	Immediate reaction Misuse, because product not recommended for children under seven years of age Allergy tests not available

3.3. Nutrivigilance case 2012-153 (Sérélys®)

3.3.1. Product composition

According to information provided by the manufacturer in 2013, one Sérélys® tablet contains 160 mg of pollen extract and 7.85 mg of vitamin E.

3.3.2. Case description

This involved a 49-year-old woman with an allergy to grass pollen. She took one tablet of Sérélys® on 7 September 2012. Within minutes, she had difficulty breathing and a feeling of swelling of the oral and nasal mucosa, suggestive of laryngeal angioedema. When combined with a generalised erythematous rash, this constitutes an anaphylactic reaction. However, she was able to swallow an antihistamine tablet (Clarityne®) and call a doctor, who gave her a tablet of another antihistamine (Polaramine®). Her symptoms then abated.

The skin-prick test was positive for a Sérélys® tablet.

This clinical picture equates to Level 3 severity on the nutrivigilance scale[18].

3.3.3. Causality

The food supplement's causality in the occurrence of allergic effects was analysed by applying the method defined in the ANSES opinion of 11 May 2011 on the development of a method for determining causality in reports of adverse reactions in nutrivigilance (ANSES 2011).

[18] The scale of severity in nutrivigilance goes from Level 1 (low severity) to Level 4 (death).

3.3.3.1. Intrinsic score

The chronological score refers to the time taken for the adverse effect to appear, its progression and its recurrence when the products are reintroduced. In this case, the onset time for the effect, which was a few minutes, was found to be compatible. Since the effect abated after discontinuation of the product and after emergency treatment, the progression was described as "suggestive". The food supplement was not reintroduced. Based on this information, the chronological score is C3[19].

The semiological score is determined after establishing a differential diagnosis for the observed effect. In this case, the skin-prick test confirmed the allergy to Sérélys®. The semiological score is therefore S3[20].

The intrinsic score, which results from the combination of the chronological score and the semiological score, is therefore I4, meaning that the food supplement was very likely responsible for the occurrence of the allergy[21].

3.3.3.2. Extrinsic score

3.3.3.2.1. Bibliographical score

The bibliographical score reflects the scientific knowledge available at the time of the search for the adverse effects reported for a product and/or its components. The following search was only concerned with adverse effects of an allergic nature.

- **Pollen**

The nature of the pollen extracts used in the Sérélys® product is unknown.

Several cases of allergies caused by the ingestion of pollens of different species (dandelion, rose, orange blossom, pollen collected by bees) have been described in the literature (Cohen *et al.* 1979, Hutt *et al.* 1989, Chaussende *et al.* 1990, Karakaya and Kalyoncu 2003, El-Qutob López *et al.* 2006, Jagdis and Sussman 2012, Choi *et al.* 2015, Shahali 2015).

The bibliographical score for pollen in general is B3[22].

- **Vitamin E**

To date, no cases published in the literature have shown any allergies caused by vitamin E ingestion.

The bibliographical score for this component is B0[23].

On the other hand, several cases of vitamin E-induced allergic contact dermatitis have been reported (Kumar and Pandhi 1985, Adams and Connolly 2010). Kosari *et al.* (2010) identified 931 of these, for which patch tests, when performed, showed sensitisation to α-tocopherol found in several products, mainly cosmetics.

[19] The chronological score ranges from C0 to C4.
[20] The semiological score ranges from S0 to S3.
[21] The intrinsic score ranges from I0 (excluded) to I4 (very likely).
[22] The bibliographical score ranges from B0 to B3. A B3 score corresponds to a notable effect.
[23] A B0 score corresponds to an effect that has never been reported.

3.3.3.2.2. Other cases recorded in the nutrivigilance database

No other cases of allergy to the food supplement Sérélys® have been reported. One case of eczema had been reported, but in the absence of specific information on chronology and the adverse effect, its causality could not be analysed.

Due to the widespread presence of vitamin E in food supplements, very many cases are recorded in the database but they have not enabled any conclusions to be drawn as to the responsibility of vitamin E in the allergic reactions identified.

No other cases of allergy likely to be associated with the consumption of food supplements containing pollen extracts in particular have been brought to the attention of ANSES.

3.4. Conclusions of the WG and the CES

ANSES received three reports of severe allergic adverse effects (Level 3 severity) likely or very likely (causality score ≥ I3) associated with the consumption of food supplements involving pollen or hive products: Gelée Royale 1000 mg® chewable tablets combined with Vitalité 4G Dynamisant® sticks, Propolia® propolis gums and Sérélys® tablets.

The CES indicates that an allergy to hive products is possible, mainly because of the presence of pollen. This presence is not generally mentioned. The consumption of foods or food supplements containing pollen or hive products should be avoided by people with asthma or an atopic predisposition and, in particular, by people allergic to pollen.

The CES encourages the reporting of any adverse effects to the nutrivigilance scheme and recommends that anyone reporting allergic adverse effects document them with the results of appropriate allergy tests.

4. CONCLUSION OF THE AGENCY

The French Agency for Food, Environmental and Occupational Health & Safety received three reports of allergic-type adverse effects with Level 3 severity involving the food supplements Gelée Royale 1000 mg® chewable tablets, Vitalité 4G Dynamisant® sticks, Propolia® propolis gums and Sérélys® tablets. The causality of these food supplements in the occurrence of the adverse effects is considered likely or very likely.

ANSES therefore adopts the recommendations of the Working Group on "Nutrivigilance" and the Expert Committee on "Human Nutrition".

The Agency points out that pollen allergy is a risk factor for allergy to hive products (royal jelly, propolis, honey). It stresses that food supplements, like normal foods, may contain allergens as ingredients or contaminants.

In general, the Agency advises consumers to:

- notify a healthcare professional of any adverse effect occurring after consumption of a food supplement;
- comply with the conditions of use specified by the manufacturer;
- avoid taking food supplements on a multiple, prolonged or repeated basis throughout the year without having sought the advice of a healthcare professional;
- exercise great vigilance with regard to improper claims or products sold outside conventional channels, particularly on the Internet.

The Agency reminds healthcare professionals of the importance of their participation in reporting cases of adverse effects they suspect of being associated with the consumption of food supplements, and invites them to report these to the nutrivigilance scheme.

Dr Roger GENET

KEYWORDS

Complément alimentaire, allergie, gelée royale, miel, propolis, pollen, ginseng, caféine, acérola, gingembre
Food supplement, allergy, royal jelly, honey, propolis, pollen, ginseng, caffeine, acerola, ginger

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ANNEX 1

Presentation of the participants

PREAMBLE: The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

WORKING GROUP

Chair

Mr Alexandre MACIUK – University Lecturer (Paris-Sud University) – Speciality: pharmacognosy

Members

Ms Catherine ATLAN – University Lecturer – Hospital Practitioner (Luxembourg Hospital Centre) – Specialities: metabolic diseases, nutrition and endocrinology

Mr Alain BOISSONNAS – Retired, University Professor – Hospital Practitioner (University Hospital Paris-Sud) – Speciality: general medicine

Ms Sabrina BOUTEFNOUCHET – University Lecturer (Paris-Descartes University) – Speciality: pharmacognosy

Mr Pierre CHAMPY – University Lecturer (Paris-Sud University) – Speciality: pharmacognosy

Mr Pascal CRENN – University Professor – Hospital Practitioner (Raymond Poincaré Hospital) – Speciality: hepato-gastroenterology

Mr Thierry HENNEBELLE – University Lecturer (Lille II University) – Speciality: pharmacognosy

Ms Raphaële LE GARREC – University Lecturer (University of Western Brittany) – Speciality: toxicology

Mr Jean-Marie RENAUDIN – Hospital Practitioner (Emilie Durkheim Hospital Centre) – Speciality: allergology

Ms Dominique Angèle VUITTON – Retired, University Professor – Hospital Practitioner (University of Franche Comté) – Specialities: allergology, hepato-gastroenterology

Mr Bernard WENIGER – Retired, University Lecturer (Strasbourg University) – Speciality: pharmacognosy

Mr Jean-Fabien ZAZZO – Hospital Practitioner, retired (Antoine Béclère Hospital – AP-HP) – Specialities: anaesthesia and resuscitation, nutrition

EXPERT COMMITTEE

The work that is the subject of this report was monitored and adopted by the following Expert Committee:

- CES on "Human Nutrition" – 2015-2018

Chair

Mr François MARIOTTI – Professor (AgroParisTech) – Specialities: metabolism of proteins, amino acids, nutritional requirements and recommendations, postprandial metabolism, cardiometabolic risk

Members

Ms Catherine ATLAN – Doctor (Luxembourg Hospital Centre) – Specialities: endocrinology, metabolic diseases

Ms Catherine BENNETAU-PELISSERO – Professor (Bordeaux Sciences Agro) – Specialities: phyto-oestrogens, isoflavones, endocrine disruptors, bone health

Ms Marie-Christine BOUTRON-RUAULT – Research Director (CESP Inserm) – Specialities: nutritional epidemiology and cancer, digestive system

Mr Jean-Louis BRESSON – University Professor – Hospital Practitioner (AP-HP Necker Hospital – Sick Children, Centre for Clinical Investigation 0901) – Specialities: epidemiology, immunology, infant nutrition, pregnant women and proteins

Mr Olivier BRUYERE – University Professor (University of Liège) – Specialities: epidemiology, public health, osteoporosis

Ms Blandine DE LAUZON-GUILLAIN – Research Manager (Inserm, CRESS, Villejuif) – Specialities: epidemiology, infant nutrition, nutrition of pregnant and breastfeeding women, public health

Ms Anne GALINIER – University Lecturer – Hospital Practitioner (Paul Sabatier University – Toulouse University Hospital) – Specialities: metabolism of adipose tissue/obesity, pathophysiology

Mr Jean-François HUNEAU – Professor (AgroParisTech) – Speciality: human nutrition

Ms Emmanuelle KESSE-GUYOT – Research Director (INRA, UMR Inserm U1153/INRA U1125/CNAM/University of Paris 13) – Specialities: epidemiology, nutrition and pathologies, nutrition and public health

Ms Corinne MALPUECH-BRUGERE – University Lecturer (University of Auvergne) – Speciality: disease nutrition, metabolism of macro- and micronutrients

Ms Catherine MICHEL – Research Manager (INRA, UMR INRA/University, Nantes) – Specialities: infant nutrition, intestinal microbiota, colic fermentation, prebiotics

Ms Beatrice MORIO-LIONDORE – Research Director (INRA Lyon) – Specialities: human nutrition, energy metabolism

Ms Jara PEREZ-JIMENEZ – Contract Researcher (ICTAN – CSIC, Madrid) – Specialities: micro-constituents, nutrition and pathologies, bioavailability

Mr Sergio POLAKOFF – Research Manager (INRA Clermont-Ferrand/Theix) – Specialities: nutrition and pathologies, nutrition and public health, energy metabolism

Mr Jean-Marie RENAUDIN – Hospital Practitioner (Emilie Durkheim Hospital Centre) – Specialities: allergology

Ms Anne-Sophie ROUSSEAU – University Lecturer (University of Nice Sophia Antipolis) – Specialities: nutrition and physical activity, bioavailability, oxidative stress

Mr Luc TAPPY – University Professor – Hospital Practitioner (University of Lausanne) – Specialities: endocrinology, metabolism of carbohydrates

Mr Stéphane WALRAND – Research Director (INRA Clermont-Ferrand/Theix) – Specialities: pathophysiology, protein metabolism and amino acids

ANSES PARTICIPATION

Scientific coordination

Ms Fanny HURET – Scientific Project Leader for Nutrivigilance – Risk Assessment Department

Ms Charlotte LEGER – Scientific Project Leader for Nutrivigilance – Risk Assessment Department

Scientific contribution

Ms Gwenn VO VAN-REGNAULT – Nutrivigilance Project Officer – Risk Assessment Department

Ms Irène MARGARITIS – Head of the Nutritional Risk Assessment Unit – Seconded University Professor (University of Nice Sophia Antipolis) – Risk Assessment Department

Administrative secretariat

Ms Virginie SADE – Risk Assessment Department