

CASE REPORT

Thaumatococcus and gum arabic allergy in chewing gum factory workers

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Thaumatococcus is a sweetener and flavor modifier commonly used in the food industry. Likewise, gum arabic is widely used as a food stabilizer and thickening agent. We report here that a powder mixture composed of 10% thaumatococcus and 90% gum arabic led to allergic symptoms in the upper airways in occupationally exposed individuals: four of eight workers of a chewing gum factory exposed to this powder mixture had pronounced rhinitis. A positive skin prick test result for pure thaumatococcus was obtained in all four individuals with rhinitis of whom two also had a positive skin prick test result for pure gum arabic and gum arabic-specific IgE. Substitution of a powdered thaumatococcus with a liquid form reduced symptoms among the rhinitic workers. Although gum arabic is a well-known potential allergen, we were unable to find prior documentation of allergic symptoms to thaumatococcus when it is used in the food industry.

KEYWORDS

allergy, food industry, gum arabic, occupational exposure, thaumatococcus

1 | INTRODUCTION

Thaumatococcus is a sweet-tasting protein that is obtained from the berries of the West African katemfe plant (*Thaumatococcus daniellii*). It is used as a low-calorie sweetener and flavor modifier. Thaumatococcus maintains sweetness on the tongue for a prolonged period and is used to improve the flavor impact of mint-flavored products and enhance the cooling effect of other assorted products. Thaumatococcus is also used to mask bitter and astringent tastes. As a food ingredient, thaumatococcus is considered to be safe for consumption.^{1,2} To our knowledge, there have been no report of sensitization or allergic reactions to pure thaumatococcus when it is used as a sweetener or flavor modifier in the food industry. However, proteins homologous to thaumatococcus, the so-called thaumatococcus-like proteins (TLPs), have been identified as critical allergens in several plant food allergies, such as those of kiwi, apple, and peach.³ In addition, TLPs have also been linked to occupational diseases, such as baker's asthma⁴ and asthma in olive oil mill workers.⁵ TLPs are produced by a wide variety of plants where they may function by efficiently preventing infections.⁶

In contrast with the largely unknown allergenic status of thaumatococcus compound, gum arabic is a relatively well-known potential allergen. Gum arabic is a mixture of mainly carbohydrates and some glycoproteins that is mainly obtained from the sap of *Acacia senegal*. It is added to drinks and food products as a thickening agent, emulsifier, and stabilizer, including in chewing gum production. It is also used as an excipient in pharmaceutical products. As a food ingredient, gum arabic is considered to be safe for consumption.⁷ The allergenic potential of gum arabic for employees in the food industry has already been described. In a Finnish candy factory, airborne exposure to gum arabic was associated with bronchial asthma in four out of eleven workers, contact urticaria in two, and rhinitis in one.⁸ Isolated cases of food allergies to other plant-based gums (eg, locust and carob bean gum) are also documented.⁹ Occupational urticaria due to locust bean flour was described in a cook who handled powder to prepare crème caramel.¹⁰ Locust bean flour was also associated with occupational rhinitis and asthma in a jam factory worker¹¹ and an ice-cream manufacturer.¹²

Both thaumatococcus and gum arabic are important additives in chewing gum production worldwide. An estimated 890 000 000 kg of chewing gum are produced globally each year, including approximately 190 000 000 kg in North America and 150 000 000 kg in Europe.¹³

Institution at which the work was performed: Suva (Swiss National Accident Insurance Fund), Division of Occupational Medicine, Lucerne, Switzerland.

In 2014, the Occupational Medicine Department at Suva (Swiss National Accident Insurance Fund), which is responsible for investigating and preventing occupational diseases, received a report from a chewing gum production plant of four cases of workplace-related upper respiratory symptoms related to a thaumatin-gum arabic powder mixture. Thaumatin has been used as a sweetener and flavor modifier in this chewing gum production plant since 2011, and in increasing quantities since 2014. Although pure gum arabic has been used in this plant since the 1970s, prior to the addition of thaumatin, no workplace symptoms associated with its use had been reported. This scenario prompted us to investigate the exposed employees.

2 | MATERIALS AND METHODS

2.1 | Subjects and workplace

We performed symptom assessment, rhinological, and pulmonary examinations and allergy testing on eight male employees, aged 23-52 (average 36) years. We conducted the investigations as part of our statutory remit; after a comprehensive briefing, the workers who had been exposed to thaumatin-gum arabic powder mixture provided their written informed consent to participate in the testing.

The chewing gum production plant employs a total of 61 persons and manufactures 4 800 000 kg of chewing gum each year. On-site investigations revealed that the four affected workers were regularly exposed to a powder mixture composed of 10% thaumatin and 90% gum arabic and to other substances in powder form (eg, acesulfam, aspartam, xylitol, isomalt, peppermint, spearmint, strawberry) during preparatory operations while they were adding raw materials and ingredients. These four individuals worked as part of a group of eight workers who all were exposed to these substances (Fig. 1).

2.2 | Substances

According to the manufacturer, the thaumatin-gum arabic powder mixture (Naturex, Avignon Cedex, France) does not contain any



FIGURE 1 Photograph of a chewing gum factory operator filling a modeling machine with a powder mixture composed of 10% thaumatin and 90% gum arabic

preservatives or other additives. The powder was free of pathogens according to microbiological monitoring (Labor Bioexam AG, Lucerne, Switzerland). Granulometric analysis revealed that the median grain size was 87 μm (Suva Analytics Section, Lucerne, Switzerland).

2.3 | Medical history

We recorded the following information while taking the workers' history: time worked in the plant in months, last exposure to thaumatin-gum arabic in days, workplace-related upper and lower respiratory symptoms (ie, sneezing, nasal obstruction, rhinorrhea, and asthma symptoms), use of topical nasal corticosteroids and/or antihistamines, atopic illnesses, known food allergies, symptoms associated with chewing gum consumption, and smoking habits.

2.4 | Skin prick tests

Skin prick tests were performed with commercially available common environmental allergens including grass, hazel, alder, birch, and mugwort pollens; *Alternaria tenuis*; house dust mites; cat epithelium; and latex (Allergopharma AG, Therwil, Switzerland). We also carried out skin prick tests with pure thaumatin (Natex UK Ltd, Hertfordshire, UK), pure gum arabic (NEXIRA Food, Rouen, France), guar gum (hospital pharmacy, University Hospital Basel, Basel, Switzerland), and locust bean gum (hospital pharmacy, University Hospital Basel).

2.5 | Anterior rhinoscopy with nasal cytology and nasal provocation test

Anterior rhinoscopy was used to assess the state of the turbinates and the color of the mucosa, and a brush biopsy was executed to obtain cytological material from the nasal mucosa at the level of the inferior turbinate. The cytological architecture of the mucosa reflects the origin of nasal disease. The brush method yields the best harvest of epithelial and immunological cells from nasal mucosa for microscopic and biochemical analysis.¹⁴ A medical specialist in cytopathology assessed the cytology test results. We performed a nasal provocation test in two of the employees with thaumatin-gum arabic powder mixture (Naturex). The other individuals declined this test.

2.6 | Spirometry

Three individuals with rhinitis but without lower respiratory symptoms underwent spirometric and plethysmographic testing (Body Master-screen CPX, Erich Jaeger GmbH, Hoechberg, Germany). The individuals have worked in the plant for 26-64 months and the last exposure to thaumatin-gum arabic mixture was 4-8 days ago. Pulmonary function test results is comparing with reference values for Caucasians. Because we stated normal dynamic and static ventilatory mechanics we abstained from retesting with bronchodilators. All tests were performed according to American Thoracic society/European Respiratory Society (ATS/ERS) guidelines for spirometry and lung volume measurement.

2.7 | Specific IgE

ImmunoCAP (Thermo Fisher Scientific/Phadia, Uppsala, Sweden) was used in accordance with the manufacturer's instructions to quantify IgE specific to gum arabic, guar gum, and locust bean gum. We considered specific IgE values of <0.35 kU/l to be negative. We could not perform ImmunoCAP testing for thaumatin because of unavailability of such test at the time of this report.

2.8 | Basophil activation test

A basophil activation test was performed on blood from two symptomatic and four asymptomatic workers. Heparinized whole blood was incubated for 15 min at 37°C with the thaumatin-gum arabic powder mixture (Naturex) in concentrations ranging from 0.01 to 100 µg/mL. Formyl-methionyl-leucyl-phenylalanine (fMLP; Sigma-Aldrich, Buchs, Switzerland), goat anti-human IgE (Sigma-Aldrich), and phosphate-buffered saline (PBS; Sigma-Aldrich) served as controls. After incubation, cells were stained with CD203c-PE (Beckman-Coulter, Nyon, Switzerland), CD45-PerCP, and CD63-FITC (BD Biosciences, San Jose, CA) for 15 min. After erythrocyte lysis and washing, cells were analyzed by flow cytometry with a FACSCanto II and FACSDiva software (BD Biosciences). Basophils were identified by their CD45 and CD203c expression profile, and basophil activation and degranulation was based on high CD63 expression.

3 | RESULTS

3.1 | Symptomatic workers

Four of the eight employees that we included in our investigation had workplace-related symptoms such as rhinorrhea, nasal obstruction, and sneezing. All of the employees stated that they did not experience any oral or gastrointestinal symptoms when chewing gum. None of the symptomatic individuals had taken topical nasal corticosteroids and/or antihistamines. All four of the symptomatic employees were smokers.

The four subjects with pronounced rhinitis showed a strong positive reaction in the skin prick test to pure thaumatin (10% weight/volume solution) (Fig. 2). After the factory replaced the powdered thaumatin with a liquid form, the symptoms have decreased in all affected workers. Two workers remained completely symptom free. They did not have IgE antibodies specific to gum arabic, and skin prick tests for pure gum arabic were negative. Two individuals were not completely symptom free and continued to report work-related rhinitis. They showed a positive reaction to the skin prick test with pure gum arabic (10% weight/volume solution) and also had IgE antibodies specific to gum arabic (Table 1).

After the factory replaced powdered thaumatin with a liquid form and suspended exposure to gum arabic powder, all of the affected individuals remained or became completely free of symptoms. Three of the four symptomatic employees also tested positive in the skin prick test for common environmental allergens (grass, alder, birch,



FIGURE 2 Photograph of skin prick tests on the forearm of one of the subjects. +, histamine; –, NaCl; 1, pure thaumatin; 2, pure gum arabic; 3, guar gum; 4, locust bean gum

house dust mites). This indicates the presence of an atopic disposition, which may have favored the development of an allergy to thaumatin and gum arabic. One of these individuals also had IgE antibodies specific to locust bean gum.

Two symptomatic individuals took part in a basophil activation test with the thaumatin-gum arabic mixture to which they had been exposed. We observed stimulation of the basophils in both cases (Table 1).

We also conducted a nasal provocation test with thaumatin-gum arabic powder mixture in two symptomatic employees, which produced significantly reduced flow, with completely blocked nasal breathing, in both cases. None of the exposed individuals experienced any lower respiratory symptoms. Three of the individuals underwent spirometric and plethysmographic testing, which confirmed normal respiratory function.

During a rhinoscopy in 2014, all four of the symptomatic individuals had nasal concha hypertrophy with inflamed nasal mucosa and transparent secretions, which reflected chronic mucosal inflammation of the nose. After the powdered thaumatin was replaced with a liquid form, the nasal concha hypertrophy with inflamed nasal mucosa returned to normal in the two employees who were only allergic to pure thaumatin. The nasal status did not change in those who were allergic to both thaumatin and gum arabic.

During the first examination in 2014, when the four symptomatic employees were still being exposed to thaumatin-gum arabic powder mixture, all four individuals had distinct goblet and basal cell hyperplasia. We did not detect eosinophils in any of our subjects.

TABLE 1 Results of allergological investigations

Worker	1	2	3	4	5	6	7	8
Age, years	27	42	36	27	23	36	52	43
Time worked in the plant, months	26	36	64	20	67	23	19	264
Work-related sneezing, nasal obstruction, or rhinorrhea with exposure to thaumatin-gum arabic powder mixture	Yes	Yes	Yes	Yes	No	No	No	No
Skin prick test ^a								
Histamine	+++	+++	+++	+++	+++	+++	+++	+++
NaCl suspension	-	-	-	-	-	-	-	-
Pure thaumatin	++++	++++	++++	++++	-	-	-	-
Pure gum arabic	++	-	++	-	-	-	-	-
Guar gum	-	-	-	-	-	-	-	-
Locust bean gum	-	-	-	-	-	-	-	-
Atopic status positive skin prick tests with 10 environmental allergens ^b	4/10	0/10	5/10	5/10	0/10	2/10	0/10	0/10
ImmunoCAP specific IgE unit: kU/L								
Gum arabic	6.35	<0.35	4.83	<0.35	<0.35	Not done	<0.35	<0.35
Guar gum	<0.35	<0.35	<0.35	<0.35	<0.35	Not done	<0.35	<0.35
Locust bean gum	<0.35	<0.35	0.84	<0.35	<0.35	Not done	<0.35	<0.35
Basophil activation test with thaumatin-gum arabic mixture	Not done	Not done	Stimulated	Stimulated	Not stimulated	Not stimulated	Not stimulated	Not stimulated

^aPositive results: Scale from one + to four +++++.^bGrass, hazel, alder, birch, mugwort, alternaria tenuis, house dust mites (D. pteronyssinus, D. farinae), cat epithelium, latex.

During the follow-up examinations in 2015 and 2016, we observed marked regression of the goblet and basal cell hyperplasia.

In 2014, two of the four symptomatic employees had squamous metaplasia. However, 5-17 months after the switch from powdered to liquid thaumatin, the metaplasia was no longer detectable.

3.2 | Symptom-free workers

Four of the eight investigated employees stated that they had not experienced any workplace-related symptoms associated with thaumatin-gum arabic powder mixture. These symptom-free workers had negative skin prick test results for pure thaumatin and pure gum arabic and a negative gum arabic-specific IgE test (Table 1). Two of the asymptomatic employees were smokers, two were nonsmokers.

A basophil activation test with a thaumatin-gum arabic mixture was performed with the four symptom-free individuals. The basophils of these employees showed no evidence of activation upon stimulation by thaumatin-gum arabic mixture (Table 1).

At a rhinoscopy in 2014, three of the four symptom-free individuals had nasal concha hypertrophy with inflamed nasal mucosa and transparent secretions. At the follow-up checks, the hypertrophy and mucosal architecture had returned to normal in one individual and remained in the other two.

During the initial examination in 2014, all four symptom-free subjects had distinct goblet and basal cell hyperplasia. Two of these individuals also had squamous metaplasia, a sign of chronic irritation and regeneration of the nasal mucosa. We observed marked regression of the goblet and basal cell hyperplasia and no squamous metaplasia in 2015 and 2016.

4 | DISCUSSION

Upon exposure periods of 2-4 years, workplace-related, thaumatin-gum arabic powder mixture-induced allergic symptoms, including rhinorrhea, nasal obstruction, and sneezing, occurred in four of the eight employees that we investigated. After the factory replaced powdered thaumatin with a liquid form and suspended exposure to gum arabic powder, all of the affected individuals remained or became completely free of symptoms.

Based on the positive skin-prick tests results for pure thaumatin in all symptomatic workers, and the fact that the work-related symptoms have decreased after the factory replaced powdered thaumatin with a liquid form, we considered the pronounced rhinitis found in four of the employees to be an occupational allergy due to thaumatin. Two of these employees also had gum arabic-induced allergic symptoms.

The absence of symptoms in the workplace prior to the introduction of thaumatin has raised the question whether thaumatin might induce cross-reactivity to gum arabic. However, this hypothesis seems very unlikely. First, thaumatin is a defined protein, whereas gum arabic is a mixture of mainly carbohydrates and some glycoproteins. The carbohydrates are predominantly composed of arabinose and galactose. The three-dimensional structure of the thaumatin protein does not show any homology to that of these sugar molecules, which make it

difficult to envisage a molecular basis for such cross-reactivity. Second, if thaumatin induced cross-reactivity to gum arabic, one would expect that individuals that react positive in the skin test to thaumatin would also react to gum arabic, which is not the case (gum arabic skin test only positive in two out of four workers that reacted to thaumatin). Finally, if cross-reactivity induced by thaumatin would be the cause for reactivity to gum arabic, then the workers would not have been sensitized to the gum arabic itself, but to thaumatin, which would not be plausible since the workers were also exposed to gum arabic itself.

The results of the basophil activation test support the hypothesis of an occupational allergy to the thaumatin-gum arabic powder mixture used in this chewing gum production plant. The basophil activation test is an excellent *in vitro* method to examine basophil reactivity (ie, sensitization) to allergens¹⁵ such as the crude allergen mixture to which the workers in the present report had been exposed.

During the first examination in 2014, all four symptomatic individuals had distinct goblet and basal cell hyperplasia and two had squamous metaplasia, which is a sign of chronic irritation and regeneration of the nasal mucosa. All four symptom-free subjects had also distinct goblet and basal cell hyperplasia. Two of these individuals also had squamous metaplasia. We did not detect nasal eosinophils in any of our subjects. It was surprising that nasal eosinophilia was not present, as it is a common feature of allergic rhinitis. But when we questioned the subjects in detail, we found that the interval between the nasal swab and the last allergen exposure or the last typical symptoms of rhinitis was 4-8 days, which could explain the absence of eosinophils.^{16,17} The fact that the cytological changes were present in both groups does not allow a conclusion about which pathways led to the changes. The cytological findings were due to allergens and/or irritants (eg, menthol, peppermint) used in chewing gum production and to nonoccupational factors (eg, smoking and environmental factors like ozone and diesel engine emissions).^{18,19} However, in the follow up examinations we could observe an improvement in the nasal cytology samples (significant reduction of goblet and basal cell hyperplasia) that is likely a consequence of the enhanced respiratory protection measures implemented at the workplace.

Three individuals with rhinitis but without lower respiratory symptoms underwent a single spirometric and plethysmographic testing. Because we stated normal dynamic and static ventilatory mechanics we abstained from retesting with bronchodilators. Because none of the exposed individuals mentioned any lower respiratory symptoms we did not make serial spirometric testing in the workplace. Because the median grain size of the mixture was 87 μm , we assume that the dust was captured in the nose and did not enter the lungs. The relatively large grain size probably also caused the thaumatin-gum arabic powder to settle quickly rather than persist as airborne dust for extended periods.

Our findings indicate that thaumatin and gum arabic powder can lead to IgE-mediated type I mucosal symptoms in the upper airways in occupationally exposed individuals. The identification of thaumatin as a novel occupational allergen suggests a need for a strategy for the identification and prevention of thaumatin allergic rhinitis in the food industry worldwide. The success of the transition from a powder to a liquid formulation points to one possible control strategy.

In summary, we have documented herewith the first cases of occupational allergy due to thaumatin. Thaumatin has strong allergenic

potential in the upper respiratory tract and appears to induce more intense allergic symptoms than gum arabic. Therefore, it requires enhanced protective measures in the workplace.

AUTHORS' CONTRIBUTIONS

After consulting the employer and employees, Mattias P. Tschannen collaborated with Ulrich Glück on the planning and implementation of the investigations and the drafting of the text. Andreas J. Bircher and Ingmar Heijnen critically reviewed and supplemented the text. Andreas Bircher was the scientific mentor for the investigation process. Claudia Pletscher provided constant support for the examinations with her lively interest.

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ETHICS APPROVAL AND INFORMED CONSENT

Suva (Swiss National Accident Insurance Fund) is the supervisory body for the prevention of occupational disease in all factories in Switzerland according to Articles 50.1 und 70 ff. VUV (Regulation on the prevention of accidents and occupational diseases). We conducted the investigations as part of our statutory remit and with the written consent, following a comprehensive briefing, of the employees exposed to thaumatin and gum arabic.

DISCLOSURE (AUTHORS)

The authors report no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

Steven Markowitz declares that he has no competing or conflicts of interest in the review and publication decision regarding this article.

DISCLAIMER

None.

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