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Respiratory Health Risks from Exposure to Dust from Soybean and Its Products

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Additional information is available at the end of the chapter

Abstract

Soybean and its processed forms have become an increasingly important part of agriculture, where they are widely used as an animal feedstuff and in an extensive range of human food products. This entails transportation from producer countries, largely the USA and South America, to importer destinations such as the EU and China. Soya is recognised as a dietary allergen, containing a number of identified allergenic proteins. Inhaled soya dust generated by occupational activities also causes respiratory health problems. Reports of "asthma epidemics" in harbour cities identified ill health in the community but were related to occupational activities of unloading/loading bulk soya without appropriate dust control measures. Inhaled allergens in already-sensitised individuals can cause a range of allergic symptoms in the eyes, nose, and respiratory tract, including occupational asthma (OA). Soybean dust can also cause health problems related to lung irritancy. Endotoxin and fungal contamination associated with soya are also potential respiratory hazards. This chapter reviews published data on ill health and symptoms from airborne exposure to allergens in dust from soybean and derivative products and the levels of exposure to dust and major allergens from a range of occupational activities. Other potential health hazards associated with soybean, such as endotoxin and fungal contamination, are also highlighted.

Keywords: soy, soybean, soya, asthmagen, allergy, occupational asthma, endotoxin

1. Introduction

Soybean (*Glycine max* (L.) Merr.) has become one of the most important, versatile globally traded commodities, being a widely used source of protein, oil, and biofuel. Its uses include as a source of protein and fibre for livestock and an alternative to meat and dairy products in

humans. Soya products are also increasingly used widely in the food industry, in particular as texturisers, emulsifiers, and protein fillers; soya flour is often added to bakery products, such as bread, biscuits, pastry, etc. Soybean oil is the second largest source of vegetable oil globally and is also used in products such as biodiesel and detergents.

Soybeans are crushed to form meal, typically used in animal feed, and oil. The hull or husk of the soybean is a by-product of soybean oil and meal production where the beans are de-hulled prior to crushing. Soya hull is also internationally traded as an animal feedstuff, providing a good source of digestible fibre, albeit of lower protein content of soya meal.

The EU imported about 18 million metric tons of soya in 2018 [1]. Approximately 90% of these imports are used to feed livestock and reflect about 28% of global soya imports. China imports approximately 88 million metric tons. Although the USA remains the largest exporter of soya, projected export growth is concentrated in South America, particularly Brazil, Argentina, Paraguay, and Bolivia. The UK imports some 3 million tons annually with more than 70% directly from Argentina and Brazil. There is also an inter-trade within Europe, with the Netherlands being an important hub. The UK imports approximately two thirds as soya meal/hulls and one third as soybeans [2]. The UK only imports a relatively small quantity of soya oil, approximately 200,000 tons. The UK does not produce biofuels to any extent from imported soya.

Therefore, there is considerable bulk transportation by sea, involving handling at ports equipped to handle bulk grains and foodstuffs. Thereafter there is onward transportation for use in the animal feed industry, further processing, and the human food sector.

However, soya is not without associated risks to health. Soya products are recognised as one of the EU's 14 major food allergens and listed in Annex II of the EU Regulation 1169/2011 on labelling of foods and UK equivalent domestic legislation [3]. It is also listed as a major food allergen by the FDA (USA) labelling regulations. As soybean and its products are used in many processed foods, it is difficult for the allergic consumer to avoid and is often classified as a "hidden allergen". Additionally, evidence from a number of sources identify proteins found in soybean and its products as respiratory allergens capable of producing a range of ocular and upper and lower respiratory symptoms, including asthma.

This chapter focuses on both published evidence and our own studies related to the respiratory risk from airborne dusts related to soya.

2. Respiratory risks from soybeans

2.1. Soybean and its products

Soybean (*Glycine max* (L.) Merr.) or soya bean is the edible seed of an annual legume of the pea family (Fabaceae). The hull or husk of the mature bean is hard and water-resistant and protects the cotyledon of the seed from damage.

The major forms of soya usually encountered in end-user countries in the EU are:

1. Soybean, after removal of hull covering the bean, containing about 40% protein and 20% fat/lipid.

2. Soya meal (see **Figure 1**). This may be of two forms: pure meal produced after de-hulling and possibly extraction of oil or with subsequent added hull to extend the product. Soybean meal made from de-hulled beans has a total protein content of approximately 40–49% and 3% fibre.

3. Soybean hull, these are often pelletised as a commercial product to make a more handleable, less dusty product (see **Figure 1**). The protein content of hull is around 9–19%, with a fibre content of 53–74%. The proteins in hull tend to be of lower molecular weight than those in pure soya meal (**Figure 2**).

4. Soya oil is produced by crushing and/or chemical extraction. Soya oil, particularly the more highly purified, is considered less allergenic due to the low concentration of soya proteins within it [4, 5]. It is used widely in food processing.

5. Soya flour—milled in a similar way to cereal flour (e.g. wheat, rye). Flours from various cereals have the propensity to be "dusty", and the control of their handling is necessary to prevent airborne exposure to flour dust and consequent health effects [6, 7]. Soya flour has become increasingly used in food processing. Allergens in soya flour have been identified and characterised [8].

Figure 2 shows electrophoresis gels of extracts of a soya hull and soya meal, respectively, after extraction at 10% w/v using 0.1% Tween 20 in phosphate buffered saline. These gels separate proteins on the basis of their molecular weights. The patterns of proteins in soya hull show considerable differences to soya meal. There is a predominance of high molecular weight proteins in meal in comparison with hull where the majority of proteins appear to be less
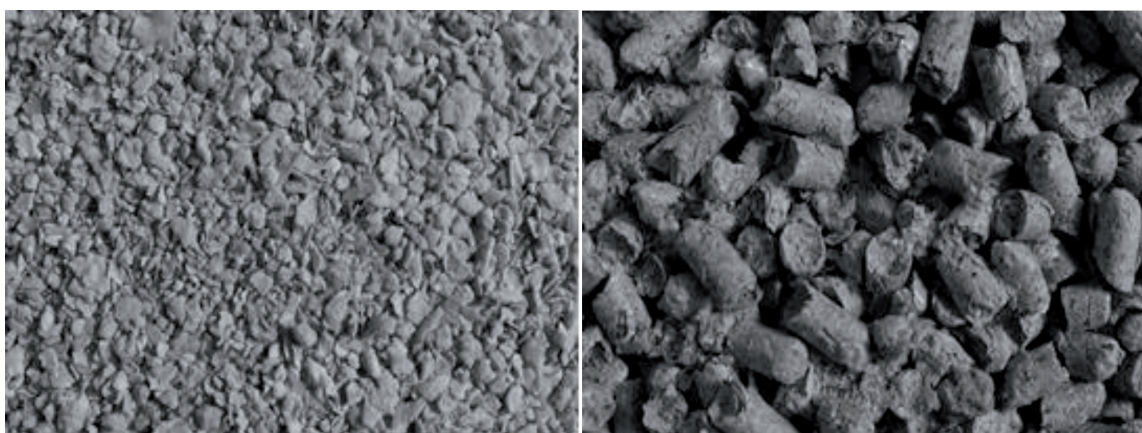

Figure 1. The left hand image shows an image of a soya meal imported in the UK. The right-hand image shows a sample of soya hull imported into the UK. The pelletised hull material shows some evidence of breakdown, probably due to compaction in the hold of the ship.
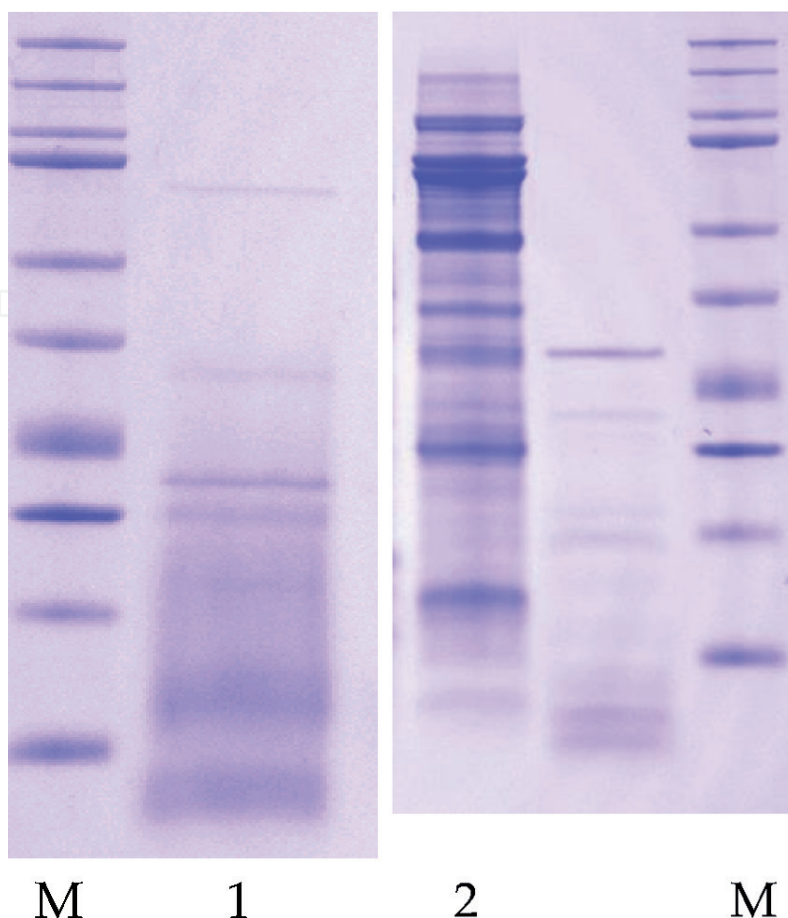
Figure 2. Left-hand gel shows a Coomassie blue-stained reducing gel of an extracted soya hull material, lane labelled 1. Right-hand gel shows a similarly stained gel of an extract of soya meal, lane labelled 2. Molecular weight marker bands for lanes marked as M have molecular weights from the top of 200, 150, 100, 75, 50, 37, 25, 20, 15, and 10 kDa.

than 23 kDa. For some soya meal products, hull is reintroduced to adjust the overall protein content, so differing soya meal imports may contain differing levels of hull proteins.

However not all proteins are allergenic, in terms of sensitising an individual's immune system to provoke an exaggerated IgE-mediated immune response on subsequent exposure to the same protein, i.e. a type 1 allergic response. Allergenic proteins appear to be restricted to classes or families of proteins based on their structural and functional properties [9–12].

2.2. Overview of intrinsic and extrinsic respiratory risk factors in soybean

However, besides intrinsic, specific allergenic proteins, covered in the next section, there are other "contaminants" or extrinsic material that may be associated with soya products and possibly lead to respiratory illnesses or symptoms, if inhaled. These include:

- Endotoxin is a pyrogenic lipopolysaccharide and a component of the exterior cell wall of gram-negative bacteria, like *E. coli*. High concentrations of airborne endotoxin can cause respiratory inflammation, symptoms, and lung function decline [13–16]. The Netherlands

has set a suggested health-based exposure limit for airborne endotoxin [17]. Endotoxin has been found to be extractable from soya meal and husk and becomes airborne when handling bulk [18–21].

• β-Glucans are naturally occurring polysaccharides, being constituents of the cell wall of certain pathogenic bacteria and almost all fungi. Their measurement in airborne samples has been used as an indicator of total fungal exposure. β-Glucans have been linked to activating macrophages, neutrophils, monocytes, and NK cells, thus involving the innate and adaptive immune systems. Biological activity seems related to their degree of branching and molecular weight; greater branching gives rise to greater biological activity, with the $(1 \rightarrow 3)$ chain essential in the induction of immune responses [22].

• Fungi such as *Aspergillus* spp., particularly the *A. glaucus* group, and *Penicillium* spp. are known as storage moulds. Contamination of batches of soya with uncontrolled fungal growth, particularly *Aspergillus* spp. and *Penicillium* spp., leads to spoilage. Certain toxicogenic *Aspergillus* species under the right conditions of moisture and temperature can lead to the production of mycotoxins and carcinogenic aflatoxins [23, 24]. In addition, *Aspergillus* and *Penicillium* species are allergenic and can also cause hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis (EAA). *Aspergillus fumigatus* can produce significant numbers of conidia (spores) containing allergenic proteins, e.g. Asp f 1, and in immune-compromised humans is the most common life-threatening, opportunistic fungal pathogen. Nonetheless, several strains of *Aspergillus* are used in the controlled fermentation of soya to produce soy sauce, including *A. oryzae*. Alpha amylase from this fungal source is used as an additive improver in cereal flour and associated with significant sensitisation in bakers [25, 26].

• Organic dust with no identifiable toxic properties can cause irritation and inflammatory responses in the lungs if the particles are small enough. Larger dust particles will lodge in the nasal passage or the throat and be cleared from the body. Particles of less than 10 μm aerodynamic diameter can enter the lungs past the bronchus, and particles less than 4 μm can reach the alveoli deep in the lungs, producing significant lower respiratory tract symptoms. Limited evidence suggests that this mechanism may be relevant for soya dust [27]. Organic dust toxic syndrome (ODTS) and EAA are distinct pathological entities associated with smaller particles below 5 μm [28]. Asthmatic reactions are generally provoked by particle sizes of 5–10 μm [29].

Of these intrinsic and extrinsic factors potentially associated with soya, it is the health effects from exposure to intrinsic soya allergens that are underpinned by significant scientific evidence. This will be the major thrust of the remainder of this chapter.

2.3. Allergens in soybean

A number of allergens have been identified and characterised in soya and its products. A 2012 OECD document on soybean allergens lists 15 proteins designated as allergens, largely derived from one literature review [12]. However there has been a criticism about the lack

of evidence for some of these "putative" allergens [30]. A non-exhaustive list of allergens is shown in the **Table 1** below. Many of the allergens were identified from a food perspective, with subsequent work to produce "hypoallergenic" cultivars [12]. While there has been considerable research on genetically modified soya with lower levels of endogenous major food allergens, a large natural variation (9–15-fold) in the levels of Gly m 4, Gly m 5, Gly m 6, Gly m Bd 28 k, and Gly m Bd 30 k has also been identified [31].

However, a much smaller number of the allergens in **Table 1** have been implicated in terms of airborne exposure during occupational practices and associated health effects.

Allergen	Description	Comments
Gly m 1	Hydrophobic soybean protein. MW 7–8 kDa with two isoforms	Abundant in soybean dust. Husk and pods are a rich source. Implicated in epidemic asthma outbreaks in harbour cities caused by soy dust [32, 33]
Gly m 2	MW 8 kDa protein with a pI 6. A member of the defensin family	Gly m 2 is abundant in soya husk and implicated in epidemic asthma outbreaks in Spanish dock cities [34]. Shows some homology with a storage protein in the cotyledon of cowpea and green pea
Gly m 3	MW 12–15 kDa protein	A profilin type of allergen. Shows some cross-reactivity with birch profilin [11, 35]
Gly m 4	MW 17 kDa. Homolog of Bet v 1, a birch allergen	Implicated as the major allergen where patients are allergic to birch pollen and have soy allergy [36]
Gly m 8	MW 28 kDa. 2S albumin	2S albumins [37]. Some homology with Ara h 2, a peanut allergen. Identified as a food allergen
Gly m 39kD	MW 39 kDa	P39 protein was detectable only in the fully mature dry seed distributed in the matrix of the protein storage vacuoles [38]
Gly m Bd28K	MW 28 kDa. A vicilin-like glycoprotein	A major food allergen [39]
Gly m Bd30K	MW 30–34 kDa protein, a thiol protease of the papain superfamily	A soybean oil body-associated glycoprotein, shows 30% sequence homology with Der p 1, a major allergen of house dust mite. An important dietary allergen, widely known as P34 [40]
Gly m Bd 60 K	MW 63–67 kDa protein	An alpha subunit of beta-conglycinin well-known as a major soybean storage protein. Major food allergen
Gly m TI	MW 20 kDa, a trypsin inhibitor	Has been implicated as a workplace inhalant allergen in bakers [41]. Found in the seed and soya flour
Gly m 5	β-Conglycinin, three isoallergens	Seed storage protein. Sensitisation to Gly m 5 is potentially indicative for severe allergic reactions to soy [42]
Gly m 6	Glycinin, five isoallergens	Sensitisation to Gly m 6 is potentially indicative for severe allergic reactions to soy [42]
Gly m 7	MW 76 kDa Seed biotinylated protein (SBP)	SBP may represent a class of biologically active legume allergens with structural resilience to many food-manufacturing processes [43]

MW refers to molecular weight.

Table 1. A non-exhaustive list of allergens identified in soya.

2.4. Published studies on health outcomes and airborne exposure to soya dust

Further airborne exposure to an allergen in an individual already sensitised can cause a range of symptoms affecting the eyes, nose, and upper and lower respiratory systems, including the development of occupational asthma (OA). OA is a disease characterised by variable airflow limitation and airway hyperresponsiveness due to a particular occupational environment. Two main types of OA are identified [44]. Immunological OA develops after a latent period of exposure during which the worker acquires sensitisation to the causal agent, typically involving IgE-mediated immunological sensitisation to allergenic proteins. Non-immunologic OA is usually due to irritant mechanisms associated with the cumulative effects of exposure to a workplace dust or chemicals. Both forms of OA can be serious enough to prevent an individual's continued employment in that workplace and even cause permanent disability.

The first study describing soya allergy related to dust from a soybean mill was published in 1934 [45]. In 1977 a study was published of immediate and late-onset OA in a previously non-allergic subject exposed to soya flour in the manufacture of food supplements [46]. Exposure to soya dust and soya flour has been implicated in causing OA or other respiratory health symptoms in persons working in a variety of occupations, such as farmers, millers, soybean processors, and bakers [8, 26, 27, 41, 45, 47, 48].

2.4.1. Asthma epidemics in harbour cities related to soya dust

In the 1990s, a number of scientific papers were published that investigated "asthma epidemics" in harbour cities, the cases of asthma being found in the general population. Investigation discovered these asthma cases were related to the loading or unloading of soya products. Reports were related to New Orleans, the USA [49], Cartagena, Spain [50, 51], Tarragon, Spain [52], Saint-Nazaire, France [53], Naples, Italy [54], Valencia, Coruna, Spain [55], and Barcelona, Spain [56].

The original outbreaks of asthma epidemics occurred in New Orleans, starting in 1953 and continuing for almost 20 years. Sometimes more than 200 people sought treatment in a single day at a hospital serving a largely black, poor population [57]. Initial investigations associated the outbreaks with low wind speeds but from a specific direction and together with particular climatic conditions. However, it was only in 1997, and after the investigations concerning Barcelona, that these community asthma outbreaks were specifically linked to the loading of soya (but not wheat or corn) into ships using an elevator system [49], suggesting that soy dust may be particularly asthmagenic compared with some grain dusts.

The asthma epidemics that occurred in Barcelona have been the best documented, and a considerable amount of research was expended in linking soya unloading at the docks with the asthma epidemics in the city, rather than other possible precipitating factors, such as traffic pollution, moulds, etc. [24, 34, 58–60]. From 1981 to 1987, 26 outbreaks of asthma occurred in the city of Barcelona, affecting a total of 687 subjects and causing 958 emergency room admissions and 20 deaths. Further outbreaks occurred in 1994 and 1996. The initial asthma

events coincided with the unloading of soya into silos without a filter, climatic conditions of high-pressure areas, and the wind direction from the harbour to the city [61].

While it might be that very specific geo-climatic conditions were the drivers for the Barcelona and other asthma epidemics, a number of important factors emerged of wider significance. Some of which were confirmed from other studies of asthma epidemics, and some of which suggested the need for further work as follows:

- The latency period from initial unloading of soya in Barcelona to asthma outbreaks appears consistent with that of occupational asthma. Children were rarely affected in these asthma epidemics, and age appeared a risk factor [62].

- The primacy of implementing exposure control measures on the occupational processes to control dust emissions and prevent further asthma outbreaks [49, 63].

- While climatic conditions may have been important, these phenomena suggest that some soya dusts generated are of a small aerodynamic diameter with high buoyancy to travel relatively large distances and penetrate deep in the lungs.

- The allergenic material identified in Barcelona implicated glycoproteins with molecular weights lower than 14 kDa, with the major allergen identified as Gly m 1 [33, 64], localised in soybean hulls/husks (see **Table 1**). Gly m 2 was also implicated [34]. Ninety-two percent of patients in the Tarragona epidemics were sensitised to soybean hull extracts [52].

- In response to the Barcelona episodes, significant effort was put into developing immunoassays capable of quantifying the putative allergen(s) with the necessary sensitivity to measure airborne levels. As with many other aeroallergen immunoassays, they progressed from initial competitive immunoassays utilising pools of serum from sensitised individuals [65] to non-competitive, sandwich assays based on polyclonal [66] or monoclonal antibodies [67]. As found for other aeroallergens, the inhibition assays are less sensitive and give considerably higher results when compared with non-competitive sandwich immunoassays [66].

- Airborne Gly m 1 levels were measured by monoclonal sandwich immunoassay, at progressive distances from Ancona's (Italy) port, where soya is unloaded [68]. Allergen concentrations were less than 171 ng m^{-3}, whereas HSP levels (highly homologous with Gly m 1 [66]) measured by sandwich immunoassay during dockside activities in Barcelona and the UK were considerably higher [19]. Decreases in allergen away from the unloading area in Ancona were detected. Airborne Gly m 1 was not coupled with the presence of soya-carrying ships in the port, but significant relationships between allergen and meteorological parameters were found, suggesting that Gly m 1 appeared part of Ancona's atmospheric dust. The authors suggest these allergen levels seem consistent with the absence of asthma epidemic outbreaks in Ancona.

- There is evidence of genetic factors, atopy, and smoking status modifying the response to exposure to soybean dust [62, 69]. Atopy and smoking have been identified as risk factors for sensitisation and work-related respiratory symptoms with a number of other occupational allergens, e.g. bakers [70], laboratory animals workers [71], and seafood processors [72, 73].

• There is evidence of co-exposure and sensitisation to some fungi and moulds, but it does not appear to have been causative of the symptoms/illnesses. Specific IgEs in a small group of asthma epidemic (AE) patients were compared with asthmatic non-epidemic patients and non-allergic controls [24]. The AE group showed low levels of specific IgE to *A. flavus*, *A. fumigatus*, *A. glaucus*, *Penicillium notatum*, and *P. chrysogenum* but significantly lower than IgE levels against soybean hull. All the AE group were sensitised to soya hull but between 8 and 92% against the moulds (*A. flavus*, *A. nidulans*, *A. glaucus*, and *P. notatum* being predominant).

2.4.2. Bakers and soybean flour

Alvarez [74] showed in a small-scale study that 25% of bakers were sensitised to soybean. A review of cross-sectional studies employing skin prick tests in bakers showed that 5–77% were sensitised to soybean flour [75]. A relatively recent UK study suggested a prevalence of 21% sensitisation using similar methodology [76]. Baur [77] found 21% serological sensitisation to soybean flour in 140 bakers who had a history of greater than 6 months of employment and work-related asthma, rhinitis, and/or conjunctivitis. Two workers were shown to be sensitised to soybean lecithin, although the lecithin was possibly contaminated with low levels of soya proteins [78]. Baur [41] studied a relatively small group of bakers both sensitised to soybean and suffering workplace symptoms. Twelve were also sensitised to wheat, ten to rye, and five to alpha amylase from *A. oryzae* (FAA). The latter being an enzyme often added to flour in small quantities, but it is now regarded as a potent allergen [25]. Baur identified soya trypsin inhibitor (STI) or Gly m T1 as a major allergen, being recognised by IgE antibodies in the sera of 86% of the examined sensitised bakers. This research was one of the drivers for the Health and Safety Executive (HSE) to develop an immunoassay sensitive enough to detect airborne levels of STI from the use of soya flour and possibly other soya products [18, 19].

In a laboratory study of components of flour improvers, a representative soya flour was neither more inherently "dusty" nor showed a shift to smaller particle sizes than three different wheat flours [79]. However, although the improvers contained a higher percentage of wheat flour than soya flour, there was roughly 10-fold more extractable STI in comparison to wheat alpha amylase inhibitor (WAAI) per unit weight of improver. WAAI is a major allergen and sensitiser in bakers, with a subunit size of around 14–16 kDa and is restricted to the seed storage tissue (endosperm) [80, 81].

Quirce [82] examined four bakers or confectioners who were sensitised to both soya and wheat using skin prick tests. A positive response to STI and FAA was noted in 2/4 cases. IgE-binding bands against soya flour showed bands at molecular weights between 25 and 55 kDa and also high molecular weight IgE-binding bands against hull extract. A case study [8] of a sensitised individual presenting with asthma after 6 years of using soya flour in food processing (not a bakery) showed immunoreactivity against nine soya proteins in the molecular weight range of 15–55 kDa. Interestingly, cross-reactivity studies with other legumes demonstrated apparent immunologic identity between a component in green pea extract and a soybean protein with a molecular weight of 17 kDa [8].

Overall these data confirm that the allergens caused by soya flour are predominantly higher molecular weight proteins, whereas the asthma epidemics in harbour cities were caused by low molecular weight proteins, specifically the allergenic proteins, Gly m1 and Gly m 2.

2.4.3. Workplaces processing soya

Early investigations in Yugoslavian soya processors by Zuskin [27, 83] studied dust inhalation and respiratory symptoms after the oil had been extracted. Exposed workers showed a considerable increase in respiratory symptoms over controls, e.g. cough, nasal symptoms, and wheezing being reported by 56, 41, and 30% of workers, respectively. Most workers were smokers, and inhalable dust levels were considerable, with a mean (range) of 29.5 (7.7–59.9) mg m^{-3}. Decreases in lung function were noted over the working week and pre-shift Monday testing suggesting evidence of chronic impairment [83]. Sixteen percent showed serological evidence of specific anti soya IgE, although 68% were positive against house dust mite. Zuskin appeared to be suggesting an irritant rather than immunologic mechanism for the airways disease.

Two related studies [21, 26] investigated sensitisation, symptoms, and exposure measurements in three South African soya processing plants. These plants were producing soya flour, based on de-hulling, cooking, and finally milling. Median (range) of inhalable dust levels were 2.58 (0.24–35.02) mg m^{-3}; STI allergen levels gave a median (range) of 70 (50–2580) ng m^{-3} and were higher in the later parts of the process. There was no significant correlation between dust levels and allergen levels. Thirty-one percent of workers were current smokers, much lower than found in Zuskin's study. There were significant associations between worked-related chest tightness, nasal symptoms, and cough/chest tightness after handling soya and sensitisation to soybean. Thirty-three percent of the workers were atopic, and 14% were sensitised to soybean not containing hull allergens. Atopy but not smoking was associated with sensitisation to soybeans, confirming the association between atopy and sensitisation to occupational allergens (Section 2.4.1).

Interestingly, Harris-Roberts reported that those transferring soybeans from farms into the processing plants' silos, where soya hull would be present, had an excess of "flu-like "symptoms of fever, aching, and tiredness [26]. Such work-related, flu-like symptoms unrelated to soya sIgE levels were also noted by Cummings, but in processors not exposed to hull [84]. The biological reason for the "flu-like" symptoms is unclear. Harris-Roberts [26] hypothesised that these symptoms may suggest organic dust toxic syndrome (ODTS) in which inhaled endotoxin has been implicated [85]. Higher levels of endotoxin are found in hull rather than soybean or soya meal [18, 19, 26], but unfortunately airborne endotoxin levels were not measured in the Harris-Roberts study. Hypersensitivity pneumonitis (HP) also called extrinsic allergic alveolitis (EAA) has been reported in a single case while handling soybean as an animal feed [86]. Both ODTS and HP can give rise to similar "flu-like" symptoms some 4–12 hours after exposure. Whatever the cause or pathology, it raises the possibility of other health problems in soya-exposed workers besides those caused by IgE-mediated sensitisation.

A study was carried out in 2007 at a US soya processing plant receiving de-oiled, de-hulled, and crushed soya flakes for further processing. Concerns had been raised about asthma and

other respiratory symptoms [48, 87]. Serum IgE immunoblotting studies showed multiple soya antigens, with 48, 54, and 62 kDa being most prominent, including storage proteins Gly m 5 and Gly m 6. As possibly expected, no sIgE to Gly m 1 or Gly m 2 was detected in this de-hulled material. The prevalence of soya specific IgE was 21% (versus 4% in controls), albeit only 7% gave a positive skin prick test for soya. Ten percent showed specific IgE towards storage mites. Those participants with soya-specific IgE had a threefold risk of current asthma or asthma-like symptoms and a six fold risk of work-related asthma symptoms. Thus asthmas and symptoms of asthma were associated with immunogenic nature of this de-hulled soya material. Work-related sinusitis, nasal allergies, and rash were also associated with reported mould exposure.

A single case study was reported from an animal feed factory, where for 5 years a man had been separating the soybean from hull before grinding [88]. He was atopic, although negative to storage mite. He showed a strong bronchial response to a challenge by soya hull but negative to soya flour. Unfortunately this short report is not clearer on the specific tasks being undertaken.

Heederik [89] studied sensitisation and respiratory effects in atopics and asthmatics (cases) living close to a Dutch soya oil producing factory. Soybeans and the oil product were transported by ship. Soya waste, after oil extraction, was removed by truck and noted to be "very dusty". Soybean unloading was carried out without any emission controls and caused visible dust clouds. Loading trucks with waste also caused dust clouds around the factory area, with spillages in transit. Only 11% of the cases were sensitised to soya by skin prick test, the same as in matched controls. Soya-sensitised individuals living in proximity to the factory reported more respiratory symptoms, used bronchodilators more often, and had poorer lung function after having been downwind of the factory. Airborne soya allergen, measured by competitive immunoassay, was found more frequently surrounding the factory with levels higher than in the control area but much lower than found on the factory premises. Periodic, high endotoxin concentrations close to the factory exceeded the suggested Dutch threshold level of 90 EU m^{-3} [17]. Interestingly only 14% of workers, although more highly exposed than the cases, were sensitised to soya, with 31% being atopic.

2.4.4. Population studies in producer countries

A study in Argentina, which is an important producer of soybeans and its products, looked at 365 cases of asthma or allergic rhinitis and 50 healthy controls. Both groups were classified as to whether they had occupational exposure to soya, were in proximity to soybean fields or grain elevators, or lived in an urban environment without obvious exposure to soybean dust [90] . The overall prevalences of sensitisation by skin prick test to soya hull in cases and controls were 15 and 0%, respectively. In the cases subdivided by exposure classification, these sensitisation prevalences were 39% (occupationally), 20% (proximity), and 8% (urban). Positive skin prick tests were higher for mites (mainly storage mites), pollen, and moulds in those positive to soya hull extract. Serological sensitisation (sIgE) to soya hull was 39 and 10% in cases and controls, respectively. The data suggest that atopic status and inhalation of soybean dust are necessary for sensitisation to soya hull. The authors opine that sensitisation

to moulds could be related to contaminated soya and noted that no near-fatal or fatal asthma had occurred, unlike the situation in epidemic asthma outbreaks involving sudden exposures to soya dust. The authors suggested that their data indicates that an immunologic mechanism rather than irritancy is responsible for soybean-induced asthma in those repeatedly exposed.

2.4.5. Studies undertaken at the Science and Research Centre of the Health and Safety Executive

Three studies were undertaken by the HSE during 2012–2017. Two studies involved occupational hygiene monitoring at different UK ports handling soya. The third study was laboratory-based, investigating inherent "dustiness" in seven imported bulk soya products. Two established allergen assays were employed: a polyclonal sandwich assay for hydrophobic seed protein (HSP) established by our collaborators in Barcelona—HSP is highly homologous with the two Gly m 1 isoallergens [66, 91]—and soya trypsin inhibitor (STI) that has been implicated as a major allergen in bakers handling soya flour [41]. Endotoxin measurements were employed to establish the extent of endotoxin contamination of soya products and the levels of airborne endotoxin that workers may inhale.

One of these studies was in response to a complaint of respiratory symptoms in a workplace situated some 300 m from a dock in the South of England. This dock is used for the unloading of soya from bulk cargo ships, its storage, and onward transport to end-users [19, 92]. Essentially, this was an occupational hygiene study but also measured the levels of soya allergen at the perimeter of the dockside operation and slightly beyond. The dock is situated to the west of a city centre of some 250,000 individuals. Containers ships are emptied by dockside grab cranes into hoppers for loading of either heavy goods vehicles for onward transportation or a conveyor belt whereby the soya was transferred to storage warehouses on-site. Concerns had been raised by the stevedores and harbour managers about the unloading of a particularly dusty batch of finely ground soya meal. But generally soya dust was visually noticeable during any unloading activity of soya meal or hull.

Samples of four different soya bulks unloaded during the study were collected. One bulk had evidence of areas of gross fungal contamination, which was identified as *Aspergillus glaucus* with moderate amounts of *Aspergillus fumigatus*. Both these fungi are common on vegetation and stored agricultural material and with sufficient available water can allow for potential heavy growth. Inhalation of these fungi is also implicated as causing hypersensitivity pneumonitis. Hull was unloaded on day 1 and meal on days 2 and 3. The hull product was a pelletised material, showing evidence of breakdown (see **Figure 1**).

The hull sample had considerably more endotoxin than meal samples (**Table 2**). While the hull sample had 15-fold more HSP than the meal, the difference in STI levels between the hull and meal was much lower. **Table 3** shows the results from static air monitoring at or outside the perimeter of the dock operation. Amounts of allergen were measurable at these peripheral sampling sites. On the day of hull unloading, significant levels of the allergen associated with asthma epidemics were measured some 150–200 m in the prevailing wind direction from where soya dust clouds were being generated.

Bulk material	Endotoxin (EU g⁻¹)	HSP (µg g⁻¹)	STI (µg g⁻¹)	Asp f 1 (µg g⁻¹)	Der p 2 (µg g⁻¹)
Pelletised hull	80,364	2824	798	Trace	Trace
Meal	4630	196	270	ND	ND
Meal, GM-free	1309	178	233	ND	ND

ND is non-detected.

Table 2. Amounts of allergens and endotoxin extracted from the three bulk samples not showing evidence of gross fungal contamination.

Site	Position	STI (ng m⁻³)	HSP (ng m⁻³)
Cruise ship customers' car park	170 m from nearest source (conveyor or hopper). In prevailing wind direction	13 (ND-40)	26 (11–125)
East end of building off-site	150–200 m from open sources. In prevailing wind direction	ND (ND-4)	87 (30–1300)[a]
Road entrance	100–150 m from sources of conveyor or hopper	19 (2–24)	54 (26–85)
Steps at boundary wall	150 m from hopper. In prevailing wind direction	56 (7–80)	339 (27–898)[a]

[a]High value associated with day of hull unloading.

Table 3. Allergen levels at the perimeter of an UK dock operation and, beyond, unloading soya.

Visual dust clouds outside were noted during various activities: (a) loading of hoppers; (b) loading of lorries from the hopper, see **Figure 3**; (c) the moving conveyor, which was subject to spillages; and (d) from craneage of soya out of the ship's holds, see **Figure 4**. Visual clouds of dust were also produced within the storage facility as the unloaded soya was formed into piles by a pusher loader or loaded into vehicles for onward transport. Respiratory protective equipment (FFP2 respirators) was worn by workers in the ship's hold, but was not uniformly worn elsewhere.

The median (range) of personal atmospheric monitoring sampling in workers over the 3 days of study were 130 (33–3071) ng m⁻³ and 583 (170–12,629) ng m⁻³ for STI and HSP, respectively. High allergen values were found when moving soya within the enclosed storage warehouses and within the ship's holds. Inhalable dust exposures (personal samples), expressed as 8 hour TWA, ranged from 1.2 to 4.5 mg m⁻³; the current UK workplace exposure limit (WEL) for flour dust and grain dust is 10 mg m⁻³. Interestingly on the day that hull was unloaded, high levels of HSP (2925 ng m⁻³) were sampled within the crane's cab although some 50 m above the dockside.

The second HSE study addressed issues concerning the likely differences in dustiness of various bulk soya products and the categorisation of the particle size of dusts generated [18]. A rotating drum testing method has been established that can investigate the generated levels of a dust under standardised conditions that are associated with the defined inhalable, thoracic, and respirable particle size fractions [93–95]. Inhalable particles of an aerodynamic diameter (AD) ≤ 100 µm can enter the respiratory tract via the nose and mouth. Thoracic sized particles

Figure 3. The visual dust cloud from a lorry loading soya from the hopper and the crane grab depositing soya into the hopper.

Figure 4. The crane is being used to move soya from the ship's hold to the dockside hoppers. Spillages and dust clouds from the crane's grab are noticeable.

(AD < 30 µm) are defined as those small enough to penetrate past the larynx as far as the trachea and bronchial areas of the lung. Respirable particles (AD < 10 µm) can enter the deeper part of the lungs.

Essentially, a fixed amount of bulk material is rotated at a set speed and time-period in a drum with vanes that lift and drop the bulk material during rotation. A constant airflow through the drum entrains any airborne dust that is collected on an in-line series of two metal foams with different pore densities and finally a glass microfibre filter. Three replicate runs with gravimetric analysis and extraction of allergens of the foams and filter are used to calculate an average dustiness in the inhalable, thoracic, and respirable sized fractions. This technique was used to compare the intrinsic dustiness in seven different bulk soya consignments recently imported into the UK and Ireland and extended to include the two major soya respiratory allergens (HSP and STI) in the generated dust fractions during dustiness testing. However, care has to be taken about not over-interpreting such results as defining actual worker exposure [96] but rather an indication of the relevant propensity of different bulks to generate dust and allergen aerosols of certain defined sizes.

The seven bulks tests included two pelletised hull and five meal bulks. None of them showed any visual fungal contamination. The mean concentration of allergens and endotoxin for meal and hull samples is shown in **Table 4**. Whereas the amount of extractable low molecular weight HSP in hull is 23-fold that in meal, there is also on average 4-fold more of 20 kDa STI in the hull product than the meal. Very low levels of the *Aspergillus fumigatus* allergen were found in all of the bulks. As reported previously [26], higher endotoxin levels tend to be found in hull than meal samples and may represent a potential additional respiratory risk [28, 85, 97].

Of the seven bulk samples, one sample showed "high" dustiness (gravimetric results) in both the thoracic and respiratory fractions compared with the other samples. This may suggest that this particular material may be the sort of bulk that produces small, buoyant dust particles that could travel further with prevailing winds and penetrate deep into the lungs to cause symptoms of irritation. Interestingly allergen concentrations in the smaller particles of this specific material did not parallel the gravimetric results. The levels of allergen in the three fractions sizes largely depend upon both the dust levels in those fractions and the amount of allergen that was readily extractable from the bulk material. So the highest concentration of HSP in small respirable particles was one of the two hull samples but generally of lower "dustiness". What is clear is that all the small respirable fractions of the seven generated dusts contained measureable but highly variable levels of allergen, and in 5/7 samples the HSP content was significantly greater than STI, even in meal samples. These data are consistent with asthma epidemics where there was distance between the point source and causation of asthma, the putative allergens being Gly m1 and Gly m 2, measured by the HSP immunoassay.

The data from the drum dustiness testing are compatible with a health risk for lung irritancy or allergic responses depending on the nature of the specific bulk material. The pelletised hull material (both of the tested hull products, **Figure 1**) seems to be largely assumed by harbour managers and importers to be a "low dust" product. However, it does show some evidence of breakdown after transportation and unloading and has higher content of low molecular weight allergens and endotoxins.

The third HSE study was an occupational hygiene survey in a different dock unloading soya, but the focus on this study was investigating the levels of airborne endotoxin, as well as the allergens STI and HSP (paper in preparation). The levels of these analytes in the unloaded

Type	STI (μg g^{-1})	HSP (μg g^{-1})	Asp f 1 (μg g^{-1})	Endotoxin (EU g^{-1})	Moisture (%)
Meal	127	122	17×10^{-3}	12,922[a]	8.3
	(28–270)	(54–196)	$(5–33) \times 10^{-3}$	(1309–51,455)	(5.2–13.9)
Hull	528	2862	13×10^{-3}	66,577	7.4
	(258–798)	(2824–2900)	$(8–19) \times 10^{-3}$	(52,769–80,364)	(6.1–8.7)

[a]Mean inflated by one high bulk value.

Table 4. Mean (range) of allergens and endotoxin extractable from the bulks and their moisture content.

bulks (hull and meal) were also measured. During both days a meal bulk was unloaded, while on the second day, a pelletised hull product was also handled that included manual cleaning or "trimming" of one of the ship's hold.

The dockside operation was very similar to the previous UK study. Bulk cargo ships were emptied using a dockside crane into a hopper, which was then used to load trailers and transported to the storage facility via a weighbridge. Inside the storage warehouse, the soya was tipped from the trailers and formed into piles, using a pusher vehicle loaded into lorries as required for onward transportation. Some lorries were also directly loaded from the hopper. In emptying the ship's hold, an excavator and Bobcat shovel loader were lowered into the hold allowing the grab crane to access material efficiently. Final "trimming" of the ship's hold was done by workers manually scraping and shovelling from the hold's sides. Spillages on the dockside were cleaned up manually and by the use of a shovel loader. Respiratory protective equipment was available to all staff and invariably worn by those working in the hold or as the hatch man, but not necessarily at other times. The excavator, crane, tractors, loading shovel, and pusher were all fitted with cab filtration.

As previously reported, higher levels of endotoxin and HSP were found in the hull bulk compared to the meal. Airborne sampling results showed geometric means (ranges) of airborne levels of dust, endotoxin, STI, and HSP during unloading of 1.6 (<1–62) mg m^{-3}, 34 (5–2450) EU m^{-3}, 146 (1–122,462) ng m^{-3}, and 608 (2–243,654) ng m^{-3}, respectively. Expressed as 8-hour TWAs, 29% of all personal samples and 100% of those involved in cleaning within the ship's hold had endotoxin levels greater than 90 EU m^{-3}, the limit for endotoxin proposed by the Netherlands [17]. All workers involved in trimming activity within the hold as part of their working day (both manually trimming and operating the excavator and Bobcat) had estimated endotoxin 8-hour TWAs of endotoxin, between 175 and 888 EU m^{-3}. Personal samples and static samples within the two vehicles involved in trimming activities suggested hold atmospheric levels of endotoxin between 275 and 2450 EU m^{-3}. Two other workers' exposure to endotoxin, when expressed as 8-hour TWAs and unrelated to trimming, breached the Dutch endotoxin guidance value. This happened on the second day, when hull was being unloaded, and is related to moving the bulk material within the storage warehouse. On day 2 when hull was being handled, there was twice as much endotoxin associated with the airborne dust collected compared with day 1.

So soya hull has higher levels of endotoxin associated with it, and considerable levels of airborne endotoxin are produced when it is handled and moved. A review of dust and

endotoxin exposure in livestock farming suggested full-shift, average levels of inhalable dust and endotoxin between 0.8–10.8 mg m^{-3} and 300–6600 EU m^{-3}, respectively [16], and a review of grain dust exposure in the UK reported a geometric mean exposure levels for endotoxin and dust of 1150 EU m^{-3} and 4.4 mg m^{-3}, respectively. Trimming activities in the ship's hold appear consistent with this level of endotoxin exposure. Swan [98], in sampling cereal grain dust exposure on the ships during unloading at two UK docks, measured endotoxin levels between 59 and 190,000 EU m^{-3} for personal samples and 74,000–7.7 x 10^6 EU m^{-3} for static samples. Swan's study found an even more highly significant association between inhalable dust and endotoxin levels than what we found. These data may suggest higher endotoxin exposure from handling cereal grain dust in these circumstances.

Table 5 compares the airborne levels of dust (gravimetric), STI and HSP, in the two occupational hygiene studies that HSE has undertaken. The static samples at the periphery of the dockside operation, and beyond, in the first study have been removed to allow better comparison. The obvious high values in the upper ranges of the second dock study likely reflect that monitoring of trimming in the hold was monitored, an obviously dusty activity.

2.5. Controlling exposure to soya dust

The evidence from the Barcelona clearly shows the value of controlling emissions of soya dust during bulk soya unloading. Such measures decreased both the measured levels of airborne soya substantially and finally eliminated outbreaks of asthma epidemic that has been serious enough to cause fatalities [63]. However, the initial implementation of control measures in 1987 still led to further outbreaks in 1994 and 1996, and in 1998 the storage silos were fitted with even greater particle retaining filters. The value of airborne monitoring of soya aeroallergens, which started in Barcelona in 1986, was also shown [56].

A number of international authoritative and regulatory bodies have recognised the health hazards from grain dust, and, while soya is not a cereal, some have explicitly encompassed soya within their definition of grain dust [99] or highlighted the similarities in the hazards (intrinsic and extrinsic) posed by dust from grain and soya [100]. A number of regulatory and authoritative bodies in the USA, Canada, and Europe have set occupational exposure

	Gravimetric dust (mg m^{-3})	STI (ng m^{-3})	HSP (ng m^{-3})
First UK dock study [19]			
Personal samples	2.0 (1.2–4.5)	130 (33–3071)	583 (170–12,629)
Workplace static samples	0.7 (0.1–5.2)	216 (11–845)	1970 (40–7438)
Second UK dock study			
Personal samples	1.8 (0.04–62.3)	178 (5–122,463)	763 (15–243,654)
Workplace static samples	1.1 (0.2–35.6)	85 (1–69,956)	318 (2–139,390)

Table 5. Geometric means (range) of airborne concentrations of gravimetric dust and soya allergens compared in the two UK dock studies. Samples are categorised as personal samples or static/background samples.

limits for grain dust ranging between 1.5 and 10 mg m^{-3} 8 hour. TWA. While Great Britain has an exposure limit for grain dust of 10 mg m^{-3} (gravimetric measurement), this is augmented by the need under the Control of Substances Hazardous to Health (COSHH) Regulations, given soya is a respiratory sensitiser, to undertake risk assessments, control soya exposures to as low as reasonable practicable, and implement appropriate health surveillance.

Monitoring by gravimetric dust is not necessarily a good surrogate of the extent of exposure to soya allergens or endotoxin. Our two dock studies [19] [paper in preparation] identified that gravimetric measurements only explained 50–70% of the variation in the airborne levels of the two allergens measured, even in a relatively constrained number of bulks. The lack of a good relationship found between gravimetric dust and allergen (HSP and STI) levels in the respiratory-sized fraction generated by drum dustiness tests confirms this [18]. HSE's second dock study suggested that gravimetric dust measurements only explained about 29–57% of the variation in endotoxin levels over the 2 days of sampling.

Issues about health risks in bakeries from exposure to cereal flour dust have been extensively investigated [6, 70, 81, 101–103], with many solutions identified for reducing bakers' exposure in terms of engineering control, local exhaust ventilation, work activity modifications, and training. Such measures to reduce airborne levels of flour should also reduce exposure to soya flour dust. Interestingly one suggestion for reducing the dustiness of certain flours, such as in improver mixes, has been the addition of soya oil [79].

3. Conclusions

The importance of soya in the global nutrition of animals and humans is well recognised. Largely cultivated in the USA or South American countries, it involves large-scale handling, processing, transportation, and finally use by a wide variety of end-users. Health problems from exposure to soya dust have been found in those directly occupationally exposed and those in the general population, indirectly exposed from occupational/agricultural activities. The major health problem seems to relate to type I, sIgE-mediated allergic reactions. There appears to be a genetic component to sensitisation; atopy status and exposure to soya dust are both significant risk factors, as well as smoking. Interestingly the reports of "flu-like" symptoms, similar to ODTS or HP, in two studies of soya processing suggest that an additional pathological mechanism can occur.

The UK largely imports soya meal and soya hull; some meal products also have an amount of hull deliberately added. The protein and allergen profiles of the two pure products are very different. Hull, which is used solely as an animal feedstuff, has a particular low molecular weight protein signature, including the two allergens Gly m 1 and Gly m 2 identified as causative in harbour city asthma epidemics. Generally, energetic handling

of hull at ports can lead to high airborne concentrations of dust containing these allergens and that can travel distances up to at least 200 m in the direction of the prevailing wind. On a smaller scale, energetic handling of hull-based animal feed may produce considerable airborne levels of allergen and endotoxin. Limited data suggest that soya products can be very different in their propensity to be dusty, the particle sizes generated, and their allergen content.

Methods for monitoring airborne levels of relevant soya allergens are available and can be used to good effect in monitoring the efficacy of control measures.

Hull products appear to have a higher endotoxin load that can be become airborne: endotoxin posing its own respiratory risks. Also poor storage conditions can lead to significant growth of fungal contamination, some of the fungal species also being associated with respiratory ill health.

Those employed and living near large-scale operations of agriculture growing soya, storing, processing, and transportation may be exposed. Occupations such as stevedores, farmers, millers, bakers, and food processors may be exposed to soya dust. Bakers, which have had significant problems with occupational asthma and allergic symptoms from cereal flour, are likely to benefit from the measures enacted to control exposure to cereal flour dust, in reducing soya exposure to soya.

Regulatory regimes that tackle issues of respiratory problems from exposure to grain dust appear to either directly or indirectly encompass soya dust. Such measures may involve setting gravimetric workplace exposure limits, although the relationship between airborne dust levels and their allergen content is not necessarily simple. Great Britain has the further regulation of COSHH for asthmagens such as soya. This mandates employers to undertake risk assessments, keep exposure to as low as reasonable practicable, and utilise appropriate health surveillance. However, the efficacy of such a regulatory framework obviously depends on its implementation where soya is encountered.

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Conflict of interest

The author declares no "conflict of interest".

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