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Review

Update on the global prevalence and severity of kiwifruit allergy: a scoping review

Christopher A. James,[1,2] Simon Welham[1] & Peter Rose[1]*

1 Division of Food, Nutrition and Dietetics, School of Biosciences, University of Nottingham, Loughborough, Leicestershire LE12 5RD, UK
2 Campden BRI, Station Rd, Chipping Campden, Gloucestershire GL55 6LD, UK

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Summary The production and use of kiwifruit, and their derived products, has seen rapid growth in the food industry with some 4 467 099 tonnes produced in 2021. A key area of development has been the increased use of kiwifruit waste streams to support sustainable food production systems. However, kiwifruit is emerging as a common elicitor of food allergy worldwide. Therefore, the present research focuses on summarising the current literature on kiwifruit-induced human food allergy. Of the available information, a total of 7098 titles were found and 107 articles were included in the current study following full-text screening. Most research concentrated on the prevalence of allergenicity and was performed within Europe, North America, Asia, Africa, South America and Oceania. Food allergy to kiwifruit ranged from oral allergy syndrome to anaphylaxis in humans. Few studies considered the need for labelling or public education. Given the increased usage of kiwifruit across a range of food streams, further research is required due to the greater focus on utilisation of these products in the food industry.

Keywords *Actinidia*, allergenicity, food allergy, food hypersensitivity, food systems, kiwi, sustainability.

Introduction

The use of fruit by-products has become one of several global trends to address sustainability within food production systems (Fierascu *et al.*, 2020; Lau *et al.*, 2021). This has led to an increase in the demand for the repurposing of food waste streams for use in other food products or cosmetics (Cassani & Gomez-Zavaglia, 2022). A group showing such versatility are fruits and waste materials derived from the genus *Actinidia*. The *Actinidia* genus comprises some 70 species, three of which are of commercial importance, namely, gold (*Actinidia chinensis*), green (*A. deliciosa*) and the hardy kiwifruit (*A. arguta*) (Huang & Ferguson, 2001; Latocha, 2017). The popularity of kiwifruits stems from them being rich sources of vitamins, minerals, carbohydrates, fatty acids, antioxidants and various phytochemicals (Richardson *et al.*, 2018). They are also reportedly high in vitamin C, vitamin E, dietary fibre, potassium, magnesium and folic acid (Tyagi *et al.*, 2015; Sivakumaran *et al.*, 2018). While the fruits are mainly consumed raw, recent interest in sustainability and circular economies has seen changes to the production systems linked to the kiwifruit industry, with proposals in the usage of kiwifruit waste tissues (pulp/skin) or extracts (Sanz *et al.*, 2021; Cairone *et al.*, 2022; Sarkar *et al.*, 2022). Currently, kiwifruit-derived materials have been increasingly used for the production of dried kiwifruit products, juices, wines, jams, jellies, vinegar, ice creams, kiwifruit seed milk, confectionary and syrups (Stanley *et al.*, 2007; Ma *et al.*, 2019; Satpal *et al.*, 2021). Moreover, justification for the usage of kiwifruit in milk cheesemaking as a chymosin alternative has been proposed (Serra *et al.*, 2020), as well as kiwifruit seeds as a substitute for soya protein, due to having better digestibility, and a better proportion of essential amino acids (Yang *et al.*, 2014). Given the interests in this fruit, it is of no surprise that the cultivation of kiwifruit and industrial production of products containing it continues to grow; however, some researchers have raised concerns regarding the allergenicity of fruits and other products that contain kiwifruit (Lucas *et al.*, 2004; Bublin, 2013; Hassan & Venkatesh, 2015).

Food allergy is a reproducible adverse reaction that takes place on exposure of an individual to a food allergen. The allergens concerned are typically proteinaceous in nature, and mediate immunologic responses *in vivo via* mechanisms, involving specific IgE (Immunoglobulin E-mediated), cell-mediated mechanisms

*Correspondent: E-mail: peter.rose@nottingham.ac.uk

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(non-Immunoglobulin E-mediated) or both IgE- and cell-mediated mechanisms (mixed IgE- and non-IgE-mediated) as described by the European Academy of Allergy and Clinical Immunology (EAACI) (Muraro *et al.*, 2014; Halken *et al.*, 2021). Food allergy is considered a clinically significant public health problem within the general population. It is currently estimated on a global basis that food allergy affects approximately 8% of children and 3%–10% of adults (Gupta *et al.*, 2018, 2019; Messina & Venter, 2020). Currently, a spectrum of diverse food items is known to be allergenic with the most commonly encountered including various tree nuts, cereals containing gluten, egg, soya, milk, crustacea and fish products, some fruits and vegetables as well as various seeds (Codex Alimentarius, 2020; FAO and WHO, 2022). Interestingly, reports of allergic reactions to kiwifruit have been documented for over 40 years and have become more common as this species is used more widely within the food industry. Given increased usage of kiwifruit in the food industry, the aim of the present review is to describe current research focused on kiwifruit-induced allergy, with emphasis on prevalence rates and clinical studies to inform practice and highlight the need for further research into kiwifruit allergenicity within food production systems.

Materials and methods

This scoping review aimed to seek primary research on the allergenicity of kiwifruit within food systems and implemented the framework defined by Arksey & O'Malley (2005) and built upon by Levac *et al.* (2010). Scoping reviews are distinct to systematic reviews, this is specifically around the research questions asked, due to scoping reviews facilitating questions that are broader and less restrictive (Arksey & O'Malley, 2005). The methods and objectives for this study have been outlined in advance, with the terms used to search the literature alongside the inclusion criteria being adjusted through the process of searching as the scope of the available literature was identified and developed.

Review questions

This scoping review pursued answers to the below questions:

1 What kiwifruit allergens have been introduced within food systems?
2 What previous research has been performed on kiwifruit allergens?
3 What are the identified health effects of these upon humans?
4 How do we address the safety of kiwifruit allergens?
5 What are the future research priorities into kiwifruit allergens?

Identification of relevant studies

To trial possible search terms, define key concepts and gain an insight into an overview of the body of literature, initially a reduced search of the literature was performed. To begin, the search terms 'Kiwifruit AND Allergy' were implemented into a search of PubMed. The titles and abstracts of the found articles were examined, resulting with several reviews being identified and read in entirety (Popovic *et al.*, 2013; Hassan & Venkatesh, 2015; Wang *et al.*, 2019, 2021). This allowed the recognition of and familiarisation with key concepts; the most researched cultivars of kiwifruit with allergenicity being incorporated into food systems, and the surrounding relevant fields of research. These concepts were employed in the development of a search matrix including keywords, subject headings and research techniques, such as truncation; to enable a systematic literature search '(Allerg*) AND (Human) AND (Kiwi) OR (Kiwifruit)', to generate results and to hone the inclusion and exclusion criteria.

The current scoping review conducted all searches within two databases (PubMed and Web of Science) applying duplicate search terms, with the most current searches being carried out on 1 August 2022.

Study selection

Inclusion and exclusion criteria

An initial search of the literature unearthed a broad variety of uses for kiwifruit within food systems (Ma *et al.*, 2019). This scoping review concentrated on the health outcomes of kiwifruit food allergens and consequently solely includes research where kiwifruit food allergens have been administered orally or *in vivo*, in humans. To enable the full available body of research to be incorporated in the review, the population age/demographic, the geographic location of study and the publication year were not restricted. Also, the language and the publication type were neither restricted before the screening stage in order to determine whether any large areas of research had not been identified due to types of articles published or languages being excluded. Food allergy to kiwifruit was defined to include all varieties of kiwifruit.

This scoping review includes:

- Primary research conducted in humans where kiwifruit food allergens had been administered *in vivo* or orally.
- All available published studies.

Research articles have been excluded if:

- Not being primary peer-reviewed studies, such as the publication type was a review, letter or editorial.

- Not written in English language.
- Studies not based on humans.
- Studies not based on food allergy to kiwifruit.
- Studies with duplicated results.

Study screening

The article screening process has been summarised in Fig. 1. Subsequent to searching the databases, the titles and abstracts were screened before applying the outlined inclusion and exclusion criteria defined above.

Charting the data

The articles selected for inclusion were read fully with the relevant data being obtained. The use of Microsoft Excel spreadsheets (tables) was applied to enable the methodical collection of the found information, including the study purpose, population and location, as well as the kiwifruit food allergens considered, how food allergy/food hypersensitivity was defined and where available the prevalence, the type of reaction and the outcomes. Scoping reviews aim to quickly highlight openings or areas where there are gaps within a research field, due to this research quality is not considered a priority for this study type (Armstrong *et al.*, 2011); therefore, searches did not employ any systematic quality assurance process. Following completion of the search, the key data and characteristics of the discovered studies were extracted into tables to allow for the straightforward comparison of their results.

Results

Eligibility and study characteristics

The literature searches identified 7098 articles, which were subsequently condensed to 309 papers through abstract and title analysis. Additional examination by the screening of the full texts allowed the elimination of 202 papers. Furthermore, a total of 3712 articles were able to be excluded as they did not relate to food allergy to kiwifruit within humans, its prevalence, burden, any education strategies or labelling information. In addition, 3262 articles were also excluded because of the publication type, namely letters to the editor, review articles and conference abstracts. An extra 15 papers were further excluded as they were not written in English, leaving 107 relevant research articles. These papers were used for data extraction and final analysis as displayed in Fig. 1.

Of the 107 included research articles, 2.8% had been published between the years (1980–1989), 15.9% (1990–1999), 37.4% (2000–2010) and 43.9% (2011–2022), which suggests an increased interest into the research of human food allergic reactions to kiwifruits and products thereof. This is likely reflective of

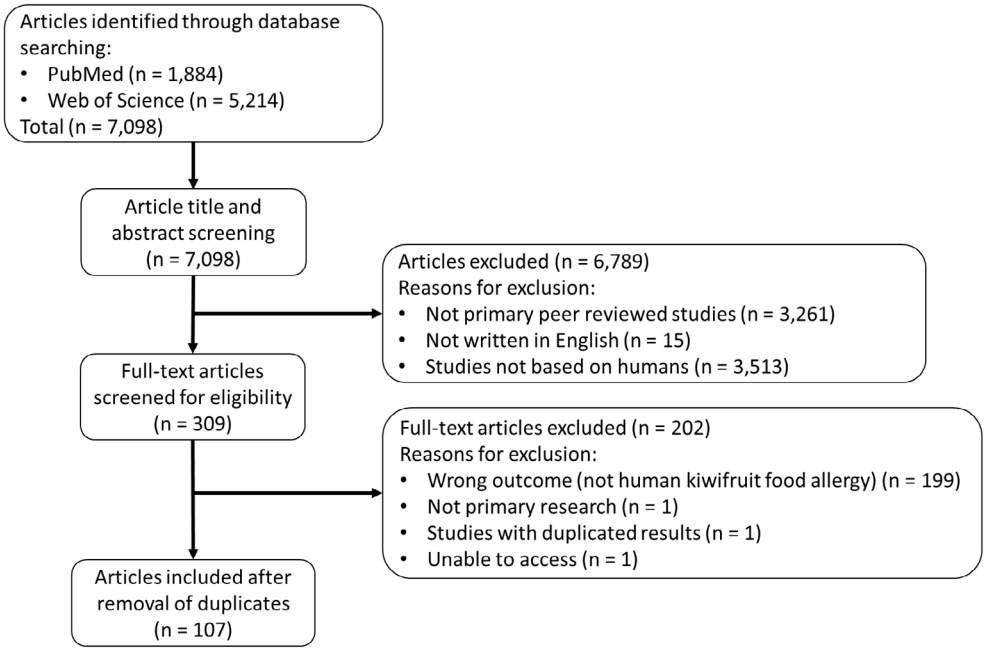

Figure 1 Flow diagram depicting the process of paper selection in the current work following the interrogation of PubMed and Web of Science, using the defined scoping review framework (Arksey & O'Malley, 2005; Levac *et al.*, 2010).

the wider utilisation of kiwifruit within the food industry, increased rates of consumption by the general public, and indicates the commercial significance of this fruit. Indeed, the commercial production of kiwifruit has grown exponentially in recent times with the main growers being the United States, New Zealand, China, Japan, Chile and European countries. The land area dedicated to the cultivation of this crop spans an area equivalent to 286 934 hectares (ha) with production rates amassing 4 467 099 tonnes (t) of fruit annually and the 2021 global mean yield per hectare has been calculated at 15.6 (t ha^{-1}) (FAO, 2023; Fig. 2). The geographic location of the studies varied with the majority (83.2%) being conducted in countries within Europe. Of the selected research articles, 56.1% are greater than a decade old, being published between 1980 and 2010. Only six of the studies were conducted in North America or Canada (5.6%) with a third of these studies being performed within the last decade (2012–2022). Similarly, 11 studies were conducted in Asia, namely, Korea, Japan and China (10.3%); one study in Australia, one study in Uganda and one study originating from Brazil. Of the 107 identified articles, 25.2% (27 of 107) considered solely younger populations (ages ranging from 0 to 18 years), 30.8% (33 of 107) adult populations (ages ranging from >18 to 96 years) and the remainder (43.9%) included both children and adults with ages spanning both ranges. Through the assessment of the 107 articles, three key research themes were identified: (1) kiwifruit food allergens, (2) prevalence of kiwifruit food allergy and (3) clinical outcomes of kiwifruit allergenicity. These identified research themes will be addressed below.

The results in this section outline that:

- A total of 7098 articles were found and following full-text screening 107 studies were included, these were published between the years (1980–2022).
- Geographic location of the studies varied, with the majority being conducted in Europe.
- Of the 107 identified studies, 25.2% considered younger populations, 30.8% considered adult populations and the remaining 43.9% included both populations.

Kiwifruit food allergens

Reports on the allergenicity to kiwifruit often indicate the symptoms to be mild and are often attributed to pollen-food syndrome (PFS), also known as oral allergy syndrome (OAS). PFS is an IgE-dependant allergic reaction demonstrating cross-reactivity between fruits and plants and is associated with allergic sensitisation to inhaled plant allergens, namely, pollen (Price *et al.*, 2015; Poncet *et al.*, 2020; Dramburg *et al.*, 2023). However, in the last decade, severe anaphylactic reactions have also been reported in the literature, and therefore, this species is of clinical importance. In addition to PFS, a link between latex allergy and cross-reactive plant-derived food allergens, latex–fruit syndrome (LFS), has also been reported in this species (Blanco, 2003; Calamelli *et al.*, 2011; Dramburg *et al.*, 2023). As shown in Table 1, 17 proteinaceous food allergens have been identified in kiwifruits and have been approved and included by the World Health

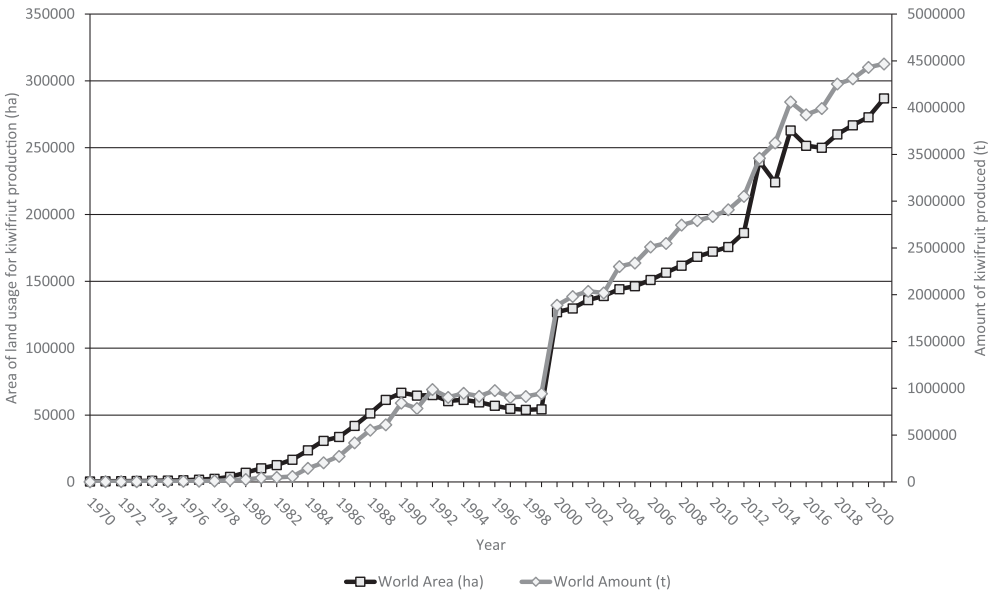

Figure 2 Growth in global kiwifruit production and land usage Food and Agriculture Organization (2023).

Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Subcommittee (see, http://www.allergen.org/); many show IgE cross-reactivity and several have been biochemically characterised. Among the identified allergens, few have been studied sufficiently in differing groups of kiwifruit-allergic patients. Allergens include Act d 1 that corresponds to the 30 kDa cysteine protease, actinidin, a well-characterised allergen in green kiwifruit (Podivinsky *et al*., 1989; Pastorello *et al*., 1998; Boland, 2013), and Act c 1 from gold kiwifruit (Lewis *et al*., 2004; Martin, 2016). Other kiwifruit allergens include Act d 2, a 24 kDa Thaumatin-like protein (TLP) (Wurms *et al*., 1999; Gavrović-Jankulović *et al*., 2002a; Alemán *et al*., 2004; Palacin *et al*., 2008a, 2011; Bublin *et al*., 2010, 2011), and putative allergens phytocystatin (Act d 4) (Rassam & Laing, 2004), kiwellin (Act d 5) found in green kiwifruit and (Act c 5) a major allergen in gold kiwifruit (Tamburrini *et al*., 2005; Tuppo *et al*., 2008; Maddumage *et al*., 2013; Offermann *et al*., 2015). In ripening of tissues, glycoprotein (Act d 3) (Palacin *et al*., 2008a; Bublin *et al*., 2010; Maddumage *et al*., 2013) and Act d 6, a pectin methylesterase inhibitor, have been identified (Camardella *et al*., 2000; Jolie *et al*., 2010; Uberti *et al*., 2015) and have demonstrated sensitisation in patients (Bublin *et al*., 2011). Several other allergens are also common in the tissues of commercial kiwifruits (Ciardiello *et al*., 2008; Oberhuber *et al*., 2008; Bublin *et al*., 2010, 2011; Bernardi *et al*., 2011; D'Avino *et al*., 2011; Agarwal & Agarwal, 2014; Sirvent *et al*., 2014a, 2014b; Nilsson *et al*., 2015; Uberti *et al*., 2015; van Odijk *et al*., 2017). A wide variation has been suggested to occur in the levels of food allergens, such as actinidin and thaumatin-like protein (TLP), across the many differing varieties of kiwifruit (Maddumage *et al*., 2013). However, a study by Blanusa *et al*. (2007) has quantified the average content of the major allergen actinidin (Act d 1), within the extracts taken from green kiwifruit (*Actinidia deliciosa*), as 0.286 mg mL^{-1} (or 62% of the total protein). Also, TLP (Act d 2) has been quantified from extracts of green (*A. deliciosa*) and gold kiwifruit (*A. chinensis*) as 0.936 (mg g^{-1}) (or 31.2% of the total protein) and 0.820 (mg g^{-1}) (or 27.3% of the total protein respectively (Gavrović-Jankulović *et al*., 2008). A study by Gavrović-Jankulović *et al*. (2008) has also demonstrated that depending on how kiwifruit have been processed and into which product, the amount of TLP that is able to be quantified can differ; 4.320 (mg g^{-1}) in kiwifruit jam in comparison to kiwifruit juice from three different manufacturers (0.135 (mg g^{-1}), 0.390 (mg g^{-1}) and 0.264 (mg g^{-1}).

The results in this section outline that:

- Within kiwifruits, 17 proteinaceous food allergens have currently been approved: 13 in green kiwifruit and 4 in gold kiwifruit.
- Food allergens in kiwifruit have been identified to have cross-reactivity with other allergens from fruits and plants.
- Wide variation is suggested to occur in the levels of food allergens across kiwifruit varieties.

Prevalence of kiwifruit food allergy

Of the 107 articles, 55 studies (51.4%) focused on prevalence of kiwifruit-associated food allergy, these results are summarised in Table S1 and include information on the population details, prevalence rates and how kiwifruit food allergy or food hypersensitivity was defined in each study. A combined total number of participants (107 675 people) represented the selected studies with an average age range of 24.4 years ±13.1 years. Almost all the studies documented prevalence (90.9%; 50 of 55) and considered a broad range of food allergies including both emerging and current allergens. Although only 5.5% (3 of 55) focused specifically on kiwifruit food allergy, with 2 considering kiwifruit in combination with other food allergens such as cereals (wheat and rye) or banana (3.6%; 2 of 55). Most prevalence studies focused on food allergy to whole kiwifruit, but few studies indicated the specific species or cultivar consumed (3 with *Actinidia deliciosa* and 2 with *Actinidia chinensis*). Interestingly, only six studies identified the individual kiwifruit allergens of interest, namely, Act d 1, Act d 2 and Act d 8 in four publications and Act d 5 in two papers.

The prevalence of food allergy to kiwifruit ranged from 0.1% to 0.2% in a birth cohort study from the Isle of Wight, in the United Kingdom. This research described the longitudinal trends and prevalence of food allergy during childhood and adolescence (Venkataraman *et al*., 2018). In another study, patients with hypersensitivity to latex and concomitant fruit sensitisation were described in those having a positive SPT to kiwifruit response (Latasa *et al*., 1995). In the studies focused solely on younger populations (ages ranging from 0 to 18 years), the prevalence of food allergy to kiwifruit ranged from 0.1% to 0.2% (Venkataraman *et al*., 2018) through to 60.0% (Vieira *et al*., 2014), see Table S1. In adult populations (ages ranging from >18 to 96 years), the prevalence of food allergy to kiwifruit ranged from 0.35% (Kim *et al*., 2018) to 38.4% (Mattila *et al*., 2003).

The 55 papers documenting prevalence of food allergy to kiwifruit are included in Table S1, these focus on the prevalence of OAS or PFS (41.8%; 23 of 55 articles), LFS (20.0%, 11 papers), involved direct immunological assessment of inflammatory markers in serum (36.4%, 20 papers) or knowledge and perception of food allergy, labelling and dietary practices (1.8%, 1 paper).

Table 1 Common food allergens in kiwifruit (http://allergen.org/)

Species	Allergen	Biochemical name	MW (SDS-PAGE/ MS*)	References
Actinidia deliciosa (Green kiwifruit)	Act d 1	Cysteine protease (Actinidin)	30 kDa	Podivinsky *et al.* (1989); Pastorello *et al.* (1998); Boland (2013)
	Act d 2	Thaumatin-like* protein	24 kDa	Gavrović-Jankulović *et al.* (2002a); Alemán *et al.* (2004); Palacin *et al.* (2008a); Bublin *et al.* (2010); Bublin *et al.* (2011); Palacin *et al.* (2011); Wurms *et al.*, 1999
	Act d 3	Glycoprotein	40 kDa	Palacin *et al.* (2008a); Bublin *et al.* (2010); Bublin *et al.* (2011); Maddumage *et al.* (2013)
	Act d 4	Phytocystatin	11 kDa	Rassam & Laing (2004)
	Act d 5	Kiwellin	28 kDa	Tamburrini *et al.* (2005); Tuppo *et al.* (2008); Offermann *et al.* (2015)
	Act d 6	Pectin methylesterase inhibitor	18 kDa	Camardella *et al.* (2000); Jolie *et al.* (2010); Bublin *et al.* (2011); Uberti *et al.* (2015)
	Act d 7	Pectin methylesterase	50 kDa	Ciardiello *et al.* (2008); Bublin *et al.* (2011)
	Act d 8	Pathogenesis-related protein, PR-10, Bet v 1 family member	17 kDa	Oberhuber *et al.* (2008)
	Act d 9	Profilin	14 kDa	Bublin *et al.* (2010)
	Act d 10	nsLTP1	10 kDa	Bernardi *et al.* (2011); Nilsson *et al.* (2015)
	Act d 11	Major latex protein/ripening-related protein (MLP/RRP), Bet v 1 family member	17 kDa	D'Avino *et al.* (2011); Uberti *et al.* (2015)
	Act d 12	Cupin, 11S globulin	50.2 kDa*	Sirvent *et al.* (2014a); Sirvent *et al.* (2014b); Nilsson *et al.* (2015); van Odijk *et al.* (2017)
	Act d 13	2S albumin	11.3 kDa*	Sirvent *et al.* (2014a); Sirvent *et al.* (2014b); Nilsson *et al.* (2015); van Odijk *et al.* (2017)
Actinidia chinensis (Gold kiwifruit)	Act c 1	Cysteine protease (Actinidin)	30 kDa	Lewis *et al.* (2004); Martin (2016)
	Act c 5	Kiwellin	28 kDa	Tamburrini *et al.* (2005); Tuppo *et al.* (2008); Maddumage *et al.* (2013)
	Act c 8	Pathogenesis-related protein, PR-10, Bet v 1 family member	17 kDa	Oberhuber *et al.* (2008)
	Act c 10	nsLTP1	10 kDa	Bernardi *et al.* (2011); Nilsson *et al.* (2015)

Key: SDS-PAGE, Sodium dodecyl sulphate polyacrylamide gel electrophoresis; MS, Mass spectrometry.
*The kDa values that have been idenified by mass spectrometry in the table.

Of the studies, 9 (16.4%) considered the prevalence of food allergy or hypersensitivity within differing geographic locations. Within the comparison of eight European countries, kiwifruit was found to be a prominent source of plant food allergy in most countries, particularly in the Netherlands, Switzerland and Spain (Lyons *et al.*, 2019, 2020). In the study by Le *et al.* (2013), comparing 12 European countries, kiwifruit and concomitant birch pollen allergy were most frequent in western and central Europe (France, northern Italy, the Netherlands, Switzerland and the United Kingdom) and that kiwifruit mono-allergy rates were higher in northern Europe (Iceland) and southern Europe (Greece and Spain). Although no explanation was given for these geographic influences.

Interestingly, a study by Dias *et al.* (2008) identified kiwifruit allergy predominantly in the non-Caucasian population, with those in this group possessing a larger number of food allergies per child, presenting with food allergy at an earlier age and having the possibility of a greater variety of food allergies when compared with Caucasians. Moreover, in the research of van Odijk *et al.* (2017), the frequency of IgE sensitisation to kiwifruit and kiwifruit seed storage proteins were higher among peanut allergic individuals. A potential link between respiratory allergy to cereal flour and allergy to kiwifruit has also been reported (Palacin *et al.*, 2008b).

As well as considering prevalence, 47 studies (85.5%) documented clinical measures being used in the assessment of kiwifruit allergy, including 31 papers that indicated the use of skin prick tests (SPTs) to assess kiwifruit allergy (56.4%) (Blanco *et al.*, 1994; Latasa *et al.*, 1995; Beezhold *et al.*, 1996; Castillo *et al.*, 1996; Rance & Dutau, 1997; Asero *et al.*, 2000; Rodriguez *et al.*, 2000; Crespo *et al.*, 2002; Florido Lopez *et al.*, 2002; Isola *et al.*, 2003; Mattila *et al.*, 2003; Roehr *et al.*, 2004; Ricci *et al.*, 2005; Asero *et al.*, 2007; Asero *et al.*, 2008; Dias *et al.*, 2008; Le *et al.*, 2008; Palacin *et al.*, 2008b; Orhan *et al.*, 2009; Osterballe *et al.*, 2009; Asero, 2011; Ferrari & Eng, 2011; Palacin *et al.*, 2011; Le *et al.*, 2013; Mustafayev *et al.*, 2013; Vieira *et al.*, 2014; Garcia and Borra, 2015; Haktanir Abul *et al.*, 2017; Kim *et al.*, 2018;

Sasaki *et al.*, 2018; Venkataraman *et al.*, 2018), 32 articles (58.2%) recognised participants having positive IgE measures (≥0.35 kUA L^{-1}) in reaction to exposure to kiwifruit (Latasa *et al.*, 1995; Castillo *et al.*, 1996; Brehler *et al.*, 1997; Rance & Dutau, 1997; Tücke *et al.*, 1999; Rodriguez *et al.*, 2000; Crespo *et al.*, 2002; Ebo *et al.*, 2003; Roehr *et al.*, 2004; Ricci *et al.*, 2005; Dias *et al.*, 2008; Le *et al.*, 2008; Palacin *et al.*, 2008b; Asero, 2011; Cremer & Mennicken, 2011; Ferrari & Eng, 2011; Palacin *et al.*, 2011; Radauer *et al.*, 2011; Le *et al.*, 2013; Vieira *et al.*, 2014; Garcia and Borra, 2015; Odongo *et al.*, 2015; van Odijk *et al.*, 2017; Sasaki *et al.*, 2018; Kim *et al.*, 2019; Lyons *et al.*, 2019; Rentzos *et al.*, 2019; Lyons *et al.*, 2020; Osawa *et al.*, 2020; Ruiz Segura *et al.*, 2020; Takemura *et al.*, 2020; Kiguchi *et al.*, 2021) and 14 studies (25.5%) applied oral challenge tests (Rance & Dutau, 1997; Tücke *et al.*, 1999; Rodriguez *et al.*, 2000; Crespo *et al.*, 2002; Florido Lopez *et al.*, 2002; Roehr *et al.*, 2004; Ricci *et al.*, 2005; Orhan *et al.*, 2009; Ferrari & Eng, 2011; Mustafayev *et al.*, 2013; Haktanir Abul *et al.*, 2017; Sasaki *et al.*, 2018; Lyons *et al.*, 2019, 2020). In addition, 11 studies (20.0%) identified characteristics of kiwifruit allergy in their assessment, with nine articles (16.4%) reporting that they assessed participants by interview (Kim & Hussain, 1999; Roehr *et al.*, 2004; Asero *et al.*, 2007; Orhan *et al.*, 2009; Asero, 2011; Mustafayev *et al.*, 2013; Vieira *et al.*, 2014; Kim *et al.*, 2019; Rentzos *et al.*, 2019) and in two studies, the treating physician present assessed kiwifruit allergy (Celakovska *et al.*, 2014; Gabrielli *et al.*, 2021). Furthermore, 29 (52.7%) of the studies used a questionnaire-based screening to scope for known symptoms of allergic reaction to kiwifruit (Eriksson, 1984; Blanco *et al.*, 1994; Castillo *et al.*, 1996; Brehler *et al.*, 1997; Kim & Hussain, 1999; Tücke *et al.*, 1999; Ebo *et al.*, 2003; Mattila *et al.*, 2003; Eriksson *et al.*, 2004; Roehr *et al.*, 2004; Rance, Grandmottet and Grandjean, 2005; Le *et al.*, 2008; Orhan *et al.*, 2009; Osterballe *et al.*, 2009; Cremer & Mennicken, 2011; Le *et al.*, 2013; Mustafayev *et al.*, 2013; Skypala *et al.*, 2013; Choi *et al.*, 2015; Haktanir Abul *et al.*, 2017; van Odijk *et al.*, 2017; Sasaki *et al.*, 2018; Lyons *et al.*, 2019; Rentzos *et al.*, 2019; Lyons *et al.*, 2020; Osawa *et al.*, 2020; Takemura *et al.*, 2020; Kiguchi *et al.*, 2021; Koga *et al.*, 2022). While surveys are useful to scope a wide range of symptoms linked to the allergenicity of kiwifruit, this style of study relies on the self-reporting of characteristics of specific food allergies by the participant or their parents/carers which could potentially introduce a perceived prevalence, therefore producing a higher prevalence rate than studies that incorporate more rigorous clinical diagnostic methods previously discussed (e.g. challenge tests) (Messina & Venter, 2020).

The results in this section outline that:

- Most prevalence studies focused on food allergy to whole kiwifruit, with few studies indicating the specific kiwifruit species, cultivar or allergen consumed.
- Prevalence of kiwifruit food allergy in younger populations ranged from 0.1%–0.2% to 60.0%.
- Prevalence of kiwifruit food allergy in adult populations ranged from 0.35% to 38.4%.

Kiwifruit clinical trials

This study identified 36 articles (33.6%) which were clinical trials and did not consider prevalence (Table S2). These investigations included a total number of participants of 2605, having a combined average age of 33.4 years ±5.1 years. The clinical trials were conducted mainly in Europe (88.9%, 32 of 36), with one study being conducted in each North America and Europe (2.8%), South America (2.8%), Japan (2.8%) and Korea (2.8%) respectively. Of these studies, 9 (25.0%) characterised and analysed kiwifruit allergens (Pastorello *et al.*, 1998; Tamburrini *et al.*, 2005; Oberhuber *et al.*, 2008; Palacin *et al.*, 2008a; Bublin *et al.*, 2010; Popovic *et al.*, 2010; Bernardi *et al.*, 2011; D'Avino *et al.*, 2011; Nilsson *et al.*, 2015), 8 (22.2%) investigated the development of kiwifruit allergy diagnostic methods (Lucas *et al.*, 2004; Bublin *et al.*, 2010; Popovic *et al.*, 2010; Bublin *et al.*, 2011; Asero, 2012; Asaumi *et al.*, 2017; Nunes *et al.*, 2019; D'Amelio *et al.*, 2021), 8 (22.2%) examined how different methods of processing or differing conditions affect the allergenicity of kiwifruit (Fiocchi *et al.*, 2004; Chen *et al.*, 2006; Bublin *et al.*, 2008; Lucas *et al.*, 2008; Bernardi *et al.*, 2010; Kim *et al.*, 2011; Grozdanovic *et al.*, 2012; Uberti *et al.*, 2015), 7 (19.4%) evaluated the comparisons and differences between differing species and cultivars (Bublin *et al.*, 2004; Lucas *et al.*, 2005; Chen *et al.*, 2006; Oberhuber *et al.*, 2008; Bernardi *et al.*, 2011; Le *et al.*, 2011; Nilsson *et al.*, 2015), 6 (16.7%) documented sensitisation to kiwifruit of different populations (Kazemi-Shirazi *et al.*, 2000; Alemán *et al.*, 2004; Lucas *et al.*, 2007; Moreno Álvarez *et al.*, 2015; Tosca *et al.*, 2015; Uberti *et al.*, 2015) and 5 (13.9%) explored the cross-reactivity of kiwifruit with other fruit, food and pollen allergens (Gall *et al.*, 1994; Pastorello *et al.*, 1996; Voitenko *et al.*, 1997; Fahlbusch *et al.*, 1998; Gavrović-Jankulović *et al.*, 2002b). The majority of the articles (47.2%) focused on allergy to characterise kiwifruit allergenic proteins, namely, Act c 1/Act d 1, 11 (30.6%) on Act c 2/Act d 2, 10 (27.8%) on Act d 5, 10 (27.8%) on Act c 8/Act d 8, 4 (11.1%) on Act c 10/Act d 10, 3 (8.3%) on Act d 3, 3 (8.3%) on Act d 4, 3 (8.3%) on Act d 11, 2 (5.6%) on Act d 6, 2 (5.6%) on

Act d 9 and 1 study (2.8%) on Act d 7. Studies by Bernardi *et al.* (2011) and Nilsson *et al.* (2015) considered allergy to kiwifruit lipid transfer proteins (LTPs) and the study by Nilsson *et al.* was the only study to explore the sensitisation pattern to seed storage proteins (11S globulin, 7S globulin and 2S albumin respectively) from both green and golden kiwifruits. Of the 36 clinical trials, 17 (47.2%) assessed kiwifruit allergens that had not been fully characterised and represented allergens ranging between 6 and 94 kDa: with these proteins being identified at 6, 15, 25, 28, 30, 34, 38, 40, 42, 58, 62 and 67 kDa (Lucas *et al.*, 2007); 8, 20, 30, 34, 38, 40, 42 and 60 kDa (Lucas *et al.*, 2005); 10–12 kDa and 20–25 kDa (Voitenko *et al.*, 1997); 11 kDa (Popovic *et al.*, 2010); 12, 14, 17, 20, 22, 24, 28, 30, 32, 38 and 41 kDa (Pastorello *et al.*, 1996); 12, 24, 30 and 66 kDa (Alemán *et al.*, 2004); 14, 17, 24 and 28 kDa (Tamburrini *et al.*, 2005); 15 kDa (Moreno Álvarez *et al.*, 2015); 17 kDa (D'Avino *et al.*, 2011); 17, 22, 24, 27, 30, 40–41, 43, 60, 67, 90 and 94 kDa (Gavrović-Jankulović *et al.*, 2002b); 20, 30, 40 and 60 kDa (Palacin *et al.*, 2008a); 21 and 28 kDa (Chen *et al.*, 2006); 23, 30, 43, 80 and 92 kDa (Fahlbusch *et al.*, 1998); 24 and 30 kDa (Fiocchi *et al.*, 2004); 24, 28 and 30 kDa protein (Pastorello *et al.*, 1998); 25 and 30 kDa (Kazemi-Shirazi *et al.*, 2000); and, 25, 28 30, 38, 40, 42, 60 and 80 kDa (Lucas *et al.*, 2008). This indicating that a spectrum of differing sized allergens is present in many kiwifruit samples.

Several clinical trials researched different species of kiwifruit; 23 (63.9%) on green kiwifruit (*Actinidia deliciosa*) (Bublin *et al.*, 2004, 2008, 2010, 2011; Fiocchi *et al.*, 2004; Lucas *et al.*, 2004, 2005, 2007, 2008; Chen *et al.*, 2006; Oberhuber *et al.*, 2008; Palacin *et al.*, 2008a; Bernardi *et al.*, 2010, 2011; Popovic *et al.*, 2010; D'Avino *et al.*, 2011; Le *et al.*, 2011; Grozdanovic *et al.*, 2012; Moreno Álvarez *et al.*, 2015; Nilsson *et al.*, 2015; Uberti *et al.*, 2015; Nunes *et al.*, 2019; D'Amelio *et al.*, 2022), 12 (33.3%) on gold kiwifruit (*Actinidia chinensis*) (Pastorello *et al.*, 1996, 1998; Gavrović-Jankulović *et al.*, 2002b; Bublin *et al.*, 2004; Lucas *et al.*, 2005; Tamburrini *et al.*, 2005; Chen *et al.*, 2006; Oberhuber *et al.*, 2008; Bernardi *et al.*, 2011; Le *et al.*, 2011; Nilsson *et al.*, 2015; Uberti *et al.*, 2015), 2 (5.6%) on hardy kiwifruit (*Actinidia arguta*) (Chen *et al.*, 2006; Kim *et al.*, 2011) and 1 (2.8%) on *Actinidia eriantha* (Le *et al.*, 2011). One notable study by Le *et al.* (2011) identified significant varietal differences in the allergenicity of six kiwifruit cultivars; *Actinidia deliciosa* cultivars 'Hayward' and 'Summer 3373', *Actinidia chinensis* cultivars 'Hort16A' and 'Jintao' and *Actinidia eriantha* cultivars 'Eriantha 96' and 'Eriantha 114'.

The majority of papers (91.7%, 33 of 36) indicated the use of IgE tests in kiwifruit food allergy assessment, 28 articles (77.8%) implemented SPTs and 17 (47.2%) applied oral challenge tests (Table S2). Only one study identified allergy using a kiwifruit buccal challenge test (Voitenko *et al.*, 1997), and another used self-reported symptoms provided by a structured questionnaire (Lucas *et al.*, 2008). The commonly documented reactions of kiwifruit allergenicity within the clinical trials included OAS (63.9%, 23 of 36 papers), gastrointestinal symptoms (47.2%), oedema (41.2%), urticarial rash (41.2%), pruritus (19.4%), anaphylaxis (16.7%), ocular (16.7%), rhinitis (16.7%), respiratory (16.7%), tightening of throat (11.1%), asthma (11.1%), flushing (8.3%) and soreness (5.6%).

The results in this section outline that:

- The clinical trials were conducted mainly in Europe.
- Of the articles, 47.2% focused on food allergy to characterised kiwifruit allergenic proteins.
- Of the studies, 47.2% assessed uncharacterised kiwifruit allergens between 6 and 94 kDa.
- Of the clinical trials, 16.7% documented anaphylaxis as an allergic reaction to kiwifruit.

Kiwifruit clinical case reports

The remaining 16 articles (15.0%) were clinical case reports (Table 2), including 37 participants with an average age range of 36.5 years ±16.0 years. Of the case reports included all but one (93.8%) used SPTs and (75.0%, 12 of 16 papers) applied IgE tests in the clinical patient assessment of food allergy to kiwifruit. These case report articles were both carried out in males and females and reported the severity of the experienced allergic reactions, which ranged from localised inflammation to anaphylactic reaction. Frequently described symptoms included pruritus (56.3%), oedema (43.8%), urticaria or erythematous (rash) (37.5%), gastrointestinal symptoms (31.3%), hypotension (31.3%), respiratory symptoms (31.3%) and anaphylaxis (31.3%, 5 of 16 papers).

The results in this section outline that:

- Of the clinical case reports, 93.8% used SPTs and 75.0% applied IgE tests in the clinical patient assessment of food allergy to kiwifruit.
- Of the studies, 31.3% documented anaphylaxis as an allergic reaction to kiwifruit.

Definitions of food allergy or food hypersensitivity used in kiwifruit Allergenicity research

Disparity in defining food allergy was found to differ significantly within the 107 research studies (Table 2; Tables S1 and S2). Interestingly, 14 (13.1%) of the included studies considered food hypersensitivity instead of using food allergy. Of these, 2 (14.3%) identified hypersensitivity as a reported history of hypersensitive

Table 2 Findings of the reviewed clinical case reports not considering prevalence of food allergy to kiwifruit

Author(s), Year	Location	Population	Definition of food allergy/food hypersensitivity	Food allergen	Type of reaction	Outcomes
Asia						
Nishie *et al.* (2021)	Japan	51-year-old female	Latex-fruit syndrome was diagnosed due to itchy mouth and lips after eating kiwi	Kiwifruit	Itchy mouth and lips	Treatment with omalizumab and food allergy symptoms disappeared
Zhu *et al.* (2012)	China	44-year-old male	Clinical symptoms and positive SPT to kiwifruit	Kiwifruit (*Actinidiaceae*)	Severe anaphylaxis generalised urticaria and dyspnoea 1 h after consuming a kiwifruit. Initially, the patient reported discrete itching of abdominal skin and was in moderate respiratory distress. SPT were performed in the patient, and result showed positive response to kiwi	Patient's wheal response and itch were attenuated 30 min after emergency treatment with intravenous antianaphylaxis drugs. However, symptoms of chest distress, dizzy, dysphoria and vital signs were exacerbated. After antianaphylaxis treatment, the patient's anaphylaxis shock symptoms were not significantly improved. After review of history, patient had eaten a full fresh kiwi, so some kiwi pulp may be left in the patient's stomach. After self-induced vomiting, the patient's clinical condition gradually improved
Europe						
Ukleja-Sokołowska *et al.* (2021)	Poland	27-year-old male	Positive SPT with fresh kiwi fruit. Positive specific IgE (CAP) $\geq$0.35 kU L^{-1}	Kiwifruit (*Actinidia deliciosa*), Act d 2	Lip swelling 5 min after eating the fruit, followed by an itchy scalp and swollen face. After 60 min, symptoms worsened: patient had generalised hives, general weakness and a 'rumbling' sensation in ears. Patient's condition improved within 25 min of having antihistamines, but the swelling of the face persisted for 24 h. The patient had previously eaten kiwi without issues. The presence of specific IgE for Act d 2 was found. Positive SPT with and specific IgE in (CAP) 0.94 kU L^{-1}	The patient was discharged with the following diagnosis: Exercise-induced anaphylaxis, food-dependent and allergic rhinitis. Patient recommended to remove kiwis from his diet. An epinephrine auto-injector was recommended to be carried on an everyday basis. The patient was educated in the management of anaphylaxis. For 6 months after hospitalisation, the patient did not experience anaphylaxis and upon a follow up visit, was advised to continue to follow previous recommendations

Table 2 (*Continued*)

Author(s), Year	Location	Population	Definition of food allergy/food hypersensitivity	Food allergen	Type of reaction	Outcomes
Ozturk & Ozyigit (2015)	Turkey	31-year-old male with a family history of kiwi allergy (anaphylaxis), Mother 55 years old and Brother 21 years old	Food allergy defined as a subject who met the criteria described below: 1) Clinical symptom criteria of a previous reaction to a food with report of clear and objective findings consisting of any one of the following symptoms: skin symptoms; respiratory tract symptoms; cardiovascular symptoms and gastrointestinal symptoms; 2) Timing of symptoms within 2 h of ingestion; 3) Specific IgE positivity or SPT (positive wheal ≥3 mm after 15 min) reactivity to culprit food	Kiwifruit	Patient had wheeze, larynx oedema and hypotension immediately after ingestion. Positive kiwi specific IgE (0.41 kU L^{-1}). Mother experienced reaction with small amount of kiwi when she was 40 years old, within a few minutes of eating kiwi developed coughing, wheezing, dyspnoea and swelling in the throat. Positive SPT (5 mm) and IgE to kiwi (1.89 kU L^{-1}). Brother reported an episode of anaphylaxis associated with kiwi ingestion at 15 years resulting in coughing, wheezing, dyspnoea and swelling in the throat. Positive SPT (3 mm) and IgE (0.69 kU L^{-1})	Following reaction patient stayed at the emergency room for 2 h with a need of epinephrine. He had not experienced any reaction to any food before and this was the first episode occurred after ingestion. Kiwi restriction in diet and epinephrine auto-injector was recommended. Asthma treatment has been started according to asthma symptom level. Mother had not eaten the kiwi in the past, and a family member provided her with an antihistamine and reaction resolved within an hour without epinephrine. She had not been exposed to kiwi after that reaction. Brother was brought to the emergency department after reaction and treated for anaphylaxis attack. Three members of the family had met all criteria and they were accepted as anaphylaxis due to kiwi allergy. Family avoided kiwi after the reactions and had no following reactions
Gawrońska-Ukleja *et al.* (2013)	Poland	55 years old, male	Positive SPT with fresh kiwifruit produced reaction equal or greater to negative control. Positive specific IgE to kiwi of class II or above	Kiwifruit	Accidental ingestion of kiwi hidden in vanilla ice cream, patient developed shortness of breath, swelling and numbness of tongue, hot flushes, dizziness and temporary loss of consciousness, involuntary urination and defecation. SPT was strongly positive. Kiwi allergy in our patient was confirmed by evaluating the level of specific IgE to kiwi 2.75 IU mL^{-1} (class II)	Symptoms subsided after taking 2 tablets of an antihistamine (cetirizine) and a tablet of calcium. The patient eliminated kiwi from his diet. We recommended the need for a 'rescue set' (adrenaline in auto syringes, oral steroids, antihistamines) and inhaled steroids to control asthma

Table 2 (*Continued*)

Author(s), Year	Location	Population	Definition of food allergy/food hypersensitivity	Food allergen	Type of reaction	Outcomes
Gázquez *et al.* (2010)	Spain	66-year-old man with a history OAS caused by kiwi	Positive SPT prick test	Kiwifruit	Acute urticaria, vomiting, chest pain and hypotension following ingestion of a piece of kiwi. SPT highly positive for kiwi, thus confirming the causal agent	The patient recovered completely, and electrocardiogram values returned to normal
Henríquez Santana *et al.* (2008)	Spain	35-year-old woman	Positive SPT produced reaction equal or greater to histamine control. Positive specific IgE $\geq$0.35 kU L^{-1}	Gold kiwifruit, Green kiwifruit	Oropharyngeal itching and generalised urticaria several minutes after ingestion of gold kiwi, previously tolerated many times. Reported severe pruritus in palms and soles, hives on trunk and extremities and dyspnoea. Uvular oedema was observed after oropharyngeal exploration and hypotension was measured. SPT with green kiwi was positive (6 mm/histamine 5 mm). SPT with gold kiwi (5 mg mL^{-1}) was positive (8 mm/histamine 5 mm). Positive specific IgE was 0.52 KU L^{-1} for green kiwi and 0.64 KU L^{-1} for gold kiwi	She received antihistamines, systemic corticosteroids and volume to improve her general state, with the symptoms disappearing within 6 h. No oral challenge was performed with green kiwi, or with gold kiwi
Kerzl *et al.* (2007)	Germany	29-year-old female with history of kiwi allergy and seasonal rhinitis during the grass pollen season	Allergy diagnosis including positive SPT (produced reaction equal or greater to histamine control) and positive specific IgE ($\geq$0.35 kU L^{-1}) to kiwi	Kiwifruit, 30-kd major kiwi allergen Act c 1	In 2006 after 4 months break from SLIT, kiwi SPT was positive, labial application test was negative, oral provocation was tolerated well without adverse reactions (dose of 1 cm^3 cube of fresh kiwi), specific IgE reduced from originally 70.4–34.6 kU L^{-1} after treatment. Western blotting with kiwi found a clearly diminished IgE-reactivity to the dominant kiwi allergen Act c 1 (30 kd)	In 2006 after 4 months break, the patient showed all criteria for a persisting state of tolerance even after the cessation of kiwi intake. Patient advised to resume the SLIT protocol without modifications (1 cm^3 kiwi cube sublingually for 1 min before swallowing). This case should encourage the consideration of SLIT protocols in patients with severe food allergies, especially in which the foods are difficult to avoid

Table 2 (*Continued*)

Author(s), Year	Location	Population	Definition of food allergy/food hypersensitivity	Food allergen	Type of reaction	Outcomes
Mempel *et al.* (2003)	Germany	29-year-old female with 15-year history of seasonal rhinitis during the grass pollen season	Allergy diagnosis including positive SPT (produced reaction equal or greater to histamine control) and positive specific IgE (≥0.35 kU L^{-1}) to kiwi	Kiwifruit, 30-kd major kiwi allergen Act c 1	Several episodes of severe anaphylaxis after consumption of kiwi, including 3 episodes of allergic shock with loss of consciousness and subsequent hospitalisation. The first 2 episodes, the symptoms started shortly after ingestion of pure fresh kiwi preparations. Anaphylaxis was elicited in the third episode by minute amounts of kiwi left on a knife used to prepare a dessert served to the patient in a restaurant. Positive specific IgE of 28.0 kU L^{-1}. Western blot analysis of kiwi revealed specific IgE reactivity to the 30 kd major kiwi allergen (Act c 1)	Because of the life-threatening nature of anaphylaxis and the impossibility of allergen avoidance, indication for immunotherapy was given, and SLIT was started in 2001 with kiwi fruit extract. Patient was administered diluted kiwi extract sublingually 3 times a day, building from 0.1 mL of a 10^{-4} dilution and gradually increased the dose in 2 h intervals, with a maximum of 3 applications per day. During increases in dose, the patient had mild (rhinitis) to severe (pharyngeal swelling, dyspnoea and nausea) symptoms, after which the dose was decreased (severe) or repeated (mild). After a dose of 1 mL of undiluted kiwi extract was reached, the patient was subsequently given a 1 cm^3 cube of fresh kiwi that was tolerated well without any adverse reactions. The patient was then advised to continue this application daily as maintenance therapy
Mancuso & Berdondini (2001)	Italy	19-year-old female with history of OAS and seasonal rhino conjunctivitis due to birch and grass pollen hypersensitivity. 2 controls	Positive clinical symptoms history. Positive SPT (produced reaction equal or greater than control)	Kiwifruit	Uvular oedema, oropharyngeal irritation and facial angioedema after kissing partner who had just eaten kiwi. The following tests were positive: (i) SPT (readings at 30 min) with partner's saliva taken 5 min after eating a kiwi fruit (ii) SPT with kiwi; (iii) RAST kiwi, The total IgE serum level was 840 IU mL^{-1}	Partner's parents (as controls) had SPT with their son's saliva, taken 5 min after eating a kiwi fruit and were negative. The means of inducing kiwi-related OAS in this case is unusual

Table 2 (*Continued*)

Author(s), Year	Location	Population	Definition of food allergy/food hypersensitivity	Food allergen	Type of reaction	Outcomes
Gastaminza *et al.* (1998)	Spain	48 -year-old male with allergy to pirazolones, rhinitis and bronchial asthma	Positive SPT produced reaction equal or greater to histamine control. Positive IgE (CAP) ≥0.35 kU L^{-1}	Kiwifruit, (*Actinidia chinensis*)	First reaction: epigastric pain, vomiting, diarrhoea and facial erythema. Second reaction: similar attack occurred after supper, abdomen was painful on deep palpation of epigastrium, without signs of peritoneal irritation. Third reaction: 1 h after a meal including a kiwi, had sudden abdominal pain in the epigastrium, radiating to the back; vomiting; pruritus; facial erythema; difficulty in breathing and conjunctival injection. Forth reaction: patient had similar symptoms, 15 min after eating a kiwi. Kiwi positive SPT (5 × 4 mm) and negative IgE	The patient was diagnosed as having pancreatitis because of allergy to kiwi. In the last 5 years, avoiding ingestion of kiwi, he has not suffered any attacks of pancreatitis or abdominal pain
Monreal *et al.* (1996)	Spain	2 patients with hypersensitivity IgE mediated to latex; 5-year-old male (patient 1) and 25-year-old female (patient 2)	Positive SPT reaction wheal was larger or the same size as histamine control. Positive specific IgE (RAST) ≥0.35 PRU mL^{-1}	Kiwifruit	Both patients had a positive SPT and specific IgE (patient 1 = 0.50 PRU mL^{-1} and patient 2 = 0.48 PRU mL^{-1}), but clinically no symptoms	Avoidance recommended to kiwifruit in order to prevent any possible reactions in the future
Novembre *et al.* (1995)	Italy	57-year-oid man	Positive SPT produced reaction equal or greater to control. Positive specific IgE ≥0.35 kU L^{-1}	Kiwifruit	Two episodes of anaphylactic shock. The first attack, which began 2–3 min after eating a piece of fruit cake (with apricot, kiwi, strawberries and grapes), was characterised by itching throat, cough, dyspnoea, hypotension and cold sweating. In the second attack, he experienced cough, itching throat. gastric pain, collapse and vomiting after eating a small piece of kiwi. Positive SPT and IgE (5.74 kU L^{-1}, class 3)	Patient recovered from both attacks without therapy

Table 2 (*Continued*)

Author(s), Year	Location	Population	Definition of food allergy/food hypersensitivity	Food allergen	Type of reaction	Outcomes
Vocks *et al.* (1993)	Germany	K.J. 26-year-old, female (Patient 1) C.D. 28-year-old, female (Patient 2)	Positive SPT reaction equal or greater to control. Positive IgE (RAST) ≥0.35 PRU mL^{-1}	Kiwifruit	Patient 1 had severe atopic dermatitis, angioedema of lips and tongue, which occurred immediately after eating kiwi. Patient 2 atopic dermatitis and allergic rhinitis with oral tingling reaction to kiwi. Both patents had a positive SPT and RAST for kiwi	The degree of cross-reactivity among kiwi, sesame seeds, poppy seeds, hazelnuts and rye grain was found to be very high in the patients studied. The existence of both cross-reacting and unique components was seen; however, the cross-reacting and unique components could be different for different patients
García *et al.* (1989)	Spain	26-year-old female without any previous allergic history, but family history of pollinic rhino conjunctivitis. 10 pollen/mite allergic and 5 healthy controls	Positive SPT reaction wheal was greater than histamine control. Positive histamine release test >16.5%. Positive specific IgE level >0.35 AEU mL^{-1}	Kiwifruit (*Actinidia chinensis*)	Reaction 1: Patient ate a small amount of kiwi and quickly had palatine, lingual, pharyngeal and otic pruritus, lasting for 15–30 min that resolved spontaneously. Reaction 2: Ate a small amount of kiwi (no more than 20 g), experienced same symptoms along with dysphagia then 15 min later, started vomiting, then had itchy wheal lesions, with spontaneous remission after 2 h. Rubbing kiwi peel on the patient's skin did not produce a reaction. SPT positive for kiwi in patient and negative in controls. Positive histamine release test (20%), negative in controls. Negative specific IgE 0.35 AEU mL^{-1} (class I)	Concluded that this was a case of mono-sensitivity to kiwi which was probably IgE mediated

Table 2 (*Continued*)

Author(s), Year	Location	Population	Definition of food allergy/food hypersensitivity	Food allergen	Type of reaction	Outcomes
North America Fine (1981)	USA	53-year-old white female	Positive hypersensitive symptoms and positive SPT (when compared to diluent control)	Kiwifruit, Chinese gooseberry (*Actinidia chinensis*)	SPT positive to kiwi skin (1:5) 3^{+}, kiwi fruit pulp (1:5) 2^{+} and positive passive transfer test kiwi fruit (1:1000) 2^{+}. Symptoms from SPT were itching, swelling and redness within 5 min. The patient began to experience a tickling throat sensation during the test	The patient was given 4 mg of Chlor-Trimeton orally and 0.2 mL of epinephrine subcutaneously. The symptoms began to subside within 10–15 min. SPT and passive transfer testing reveal that reactions to kiwi fall into the category of immediate hypersensitivity, most likely IgE mediated

Key: SLIT, Sublingual swallow allergen immunotherapy; SPT, Skin prick test; OAS, Oral allergy syndrome; PFAS, Pollen food allergy syndrome; PFS, Pollen-food syndrome; IgE, Immunoglobulin E (IgE) are antibodies produced by the immune system. If you have an allergy, your immune system overreacts to an allergen by producing antibodies called Immunoglobulin E (IgE). These antibodies travel to cells that release chemicals, causing an allergic reaction; CAP, ImmunoCAP™ tests provide an objective measurement of the circulating allergen-specific IgE antibodies. Specific IgE antibodies appear as a result of exposure and following sensitisation to an allergen; AR, Allergic rhinitis; AD, Atopic dermatitis; PR, Pathogenesis-related; RAST, Radioallergosorbent test.

reactions, 4 (28.6%) used a questionnaire to capture only self-reported adverse reactions, 6 (42.8%) studies required a positive SPT result and/or a positive specific IgE level and 2 (14.3%) studies defined hypersensitivity as a positive SPT and the reporting of hypersensitive symptoms through a taken history or self-reported by questionnaire.

The articles that remain (86.9%, 93 of 107) defined food allergy in a variety of ways, with the most often reported as being a grouping of a positive specific IgE level and a positive SPT (27.1%, 29 of 107). It was also common for studies to combine having a positive SPT result and/or a positive specific IgE level with an adverse reaction to a food allergen (18.7%; 20 of 107). Of the studies, 15 (14.0%) required a positive SPT result, a positive specific IgE level and a positive open oral challenge or double-blind placebo-controlled food challenge (DBPCFC), with a further five studies (4.7%) also including a reported history of allergy positive symptoms. A further 12 articles (11.2%) identified food allergy *via* a positive specific IgE level and another 6 (5.6%) only with a positive SPT. Additional studies had defined food allergy as an adverse reaction that was only self-reported (8.4%, 9 of 107), which included symptoms of OAS or PFAS and LFS. The remaining studies reported food allergy as a positive SPT and oral challenge (1.9%, 2 of 107), positive reported allergy symptoms, SPT and oral challenge (1.9%), positive reported allergy symptoms, specific IgE level and oral challenge (1.0%, 1 of 107), positive reported history of allergy and DBPCFC (1.0%), positive history of OAS, SPT and buccal challenge test (1.0%) and exclusively a positive oral challenge (1.0%) or a positive DBPCFC respectively.

The results in this section outline that:

- The definitions of food allergy or food hypersensitivity were found to differ significantly.
- Of the 107 studies, 13.1% considered food hypersensitivity instead of using food allergy.
- Of the 107 publications, 86.9% considered food allergy, with 27.1% of these defining it as a grouping of a positive specific IgE level and SPT.

Discussion

Kiwifruit species are nutritious and a good source of various vitamins (vitamin C, vitamin E, vitamin K and B vitamins; folate (B9), pantothenic acid (B5), pyridoxine (B6), niacin (B3), thiamine (B1) and riboflavin (B2) and minerals (copper, potassium, magnesium, manganese, calcium, phosphorus and iron) (Stonehouse *et al.*, 2013; López-Sobaler *et al.*, 2016; Richardson *et al.*, 2018; Sivakumaran *et al.*, 2018; Rasheed, Hussain and Syed, 2021). As well as these micronutrients kiwifruit contain a range of phytochemicals and

antioxidants with reported health benefits including carotenoids, lutein, caffeic acid glucosyl derivatives, β-sitosterol, quinic acid, β-carotene, zeaxanthin, chlorophylls, chlorogenic acid and phenolic compounds, such as flavones and flavanones (Park *et al.*, 2014; Leontowicz *et al.*, 2016; Pérez-Burillo *et al.*, 2018; Ozen *et al.*, 2019; Kim *et al.*, 2020; Siddique *et al.*, 2021). Kiwifruits are also high in dietary fibre, containing both soluble (pectic polysaccharides) and insoluble sources (cellulose and haemicellulose), and have been shown to support healthy intestinal motility and maintenance of normal defecation (Dimidi & Staudacher, 2020; Antonelli & Donelli, 2021; European Food Safety Authority Panel on Nutrition, Novel Foods and Food Allergens, *et al.*, 2021). Further health benefits of kiwifruit have been identified, such as reducing the risk of diabetes and cancer, boosting the immune system, facilitating the absorption of iron and vitamin D, supporting foetal development, maintaining the health of the cardiovascular and digestive systems in addition to that of the hair, eyes, skin, bone and teeth (Singletary, 2012; Latocha, 2017; Dwivedi *et al.*, 2020).

These beneficial traits coupled to consumer demand have spawned growth globally in the kiwifruit products market, with new food and drink product launches containing kiwifruit displaying a 391.7% increase, from 36 in 2002 to 177 in 2022 (Mintel, 2023). In turn, these attributes have driven the value, and range of new products that kiwifruit are used in such as ice cream, smoothies, pasta and beverages (Sun-Waterhouse *et al.*, 2013; Park *et al.*, 2016; Tylewicz *et al.*, 2020; Osoś *et al.*, 2022). Moreover, consideration of waste streams has led to the development of applied methods of processing within the food industry (Jaeger *et al.*, 2003; Jaeger & Harker, 2005; Goksel & Atak, 2014; Guroo *et al.*, 2017). In the interests of global sustainability and the repurposing of sources of food waste, the waste streams from kiwifruit production, including kiwifruit that are not of sufficient quality grade for fresh market, have provided the raw materials for the advancement of jam, butter, candy, toffee, kiwifruit leather and dried snack products (Vaidya *et al.*, 2006; Tylewicz *et al.*, 2022). This surplus kiwifruit waste has also been identified for use as a source of natural functional ingredients with benefits for human health (Sun-Waterhouse *et al.*, 2009; Dias *et al.*, 2020).

The potential for kiwifruit to have allergenicity and induce allergic reactions as a food allergen has been found to be well reported within the literature (summarised in Table 2; Tables S1 and S2). Studies demonstrated that allergenicity of kiwifruit is often attributed to PFS, which is also known as OAS and related to allergens, such as Act d 8, Act c 8, Act d 9 and Act d 11. Some cross-reactivity with allergens found in plant pollen, especially trees and grasses, has also been noted (Gall *et al.*, 1994; Pastorello *et al.*, 1996; Fahlbusch *et al.*, 1998; Mancuso & Berdondini, 2001; Gavrović-Jankulović *et al.*, 2002b; Bublin *et al.*, 2004, 2008; Fiocchi *et al.*, 2004; Lucas *et al.*, 2007; Gázquez *et al.*, 2010; Popovic *et al.*, 2010; Grozdanovic *et al.*, 2012). In addition, LFS has also been identified in those that are allergic to kiwifruit due to food allergens, such as Act d 3, Act d 7, Act d 9, Act d 11, (Bublin, 2013; Le & Knulst, 2015; Wang *et al.*, 2019, 2021) and their cross-reactivity with plant-derived allergens from the rubber tree (*Hevea brasiliensis*), such as Hev b 5, Hev b 6, Hev b 8 and Hev b 11 (Gawchik, 2011; Jiménez-Carrillo *et al.*, 2022; Dramburg *et al.*, 2023) responsible for latex allergy (Beezhold *et al.*, 1996; Monreal *et al.*, 1996; Brehler *et al.*, 1997; Kim & Hussain, 1999; Tücke *et al.*, 1999; Ebo *et al.*, 2003; Isola *et al.*, 2003; Cremer & Mennicken, 2011; Radauer *et al.*, 2011; Asero, 2012; Skypala *et al.*, 2013; Nishie *et al.*, 2021). However, the present study did not find any reports of kiwifruit inducing aeroallergy in humans. Despite some allergic reactions to kiwifruit being recorded as mild, multiple studies indicate severe allergic reactions and anaphylaxis to kiwifruit (Blanco *et al.*, 1994; Novembre *et al.*, 1995; Kazemi-Shirazi *et al.*, 2000; Florido Lopez *et al.*, 2002; Mempel *et al.*, 2003; Asero *et al.*, 2007; Palacin *et al.*, 2008a; Bernardi *et al.*, 2010; Popovic *et al.*, 2010; Zhu *et al.*, 2012; Nilsson *et al.*, 2015; Ozturk & Ozyigit, 2015; Tosca *et al.*, 2015; Asaumi *et al.*, 2017; Gabrielli *et al.*, 2021; Ukleja-Sokoowska *et al.*, 2021; D'Amelio *et al.*, 2022).

It has also been documented that kiwifruit allergenicity can be affected through different methods of processing, with some kiwifruit allergens such as Act d 1 and Act d 2 being found to be thermally unstable as well as Act d 2 being found to be more sensitive to the application of microwave and enzyme (e.g. pepsin) processing than Act d 1 (Wang *et al.*, 2019, 2021, 2023). Although when gastrointestinal digestion methods were applied to these kiwifruit allergens, they displayed nearly unchanged IgE-binding abilities (Bublin *et al.*, 2008). It was also documented in a study by Grozdanovic *et al.* (2012) that when thermally inactivated Act d 1 still exhibited IgE reactivity both *in vivo* and *in vitro*, indicating that heat processed kiwifruit products may induce other clinical reactivity and that as well as the allergenic epitopes on its surface, actinidin also contains hidden epitopes inside the protein which become accessible to IgE antibodies upon thermal treatments. In addition, further kiwifruit allergens, Act d 7 and Act d 8, have been identified as being sensitive to treatments with ethylene (Wang *et al.*, 2019, 2021). Whereas kiwifruit allergens found in the seeds have been documented as having a high resistance to thermal processing and being stable, Act d 12 and Act d 13 respectively (Wang *et al.*, 2021).

Further evidence has demonstrated that new technological methods of processing such as using high-intensity ultrasound can also induce conformational and structural changes within kiwifruit allergens (Wang *et al*., 2019). Although more conventional methods of processing such as boiling alone were not able to eliminate the reactivity in kiwifruit allergens and upon testing the most sensitised subjects were still found to react (Uberti *et al*., 2015). However, it has been specified by the Codex Alimentarius (2020) that allergens need to be managed throughout the food chain and that treatments (e.g. heating or high pressure processing) or processes that degrade proteins (e.g. enzymatic or acid hydrolysis) should not be relied upon to eliminate or completely destroy allergenic proteins.

Although there is no cure for food allergy to kiwifruit, treatments such as modified sublingual immunotherapy (SLIT) specific to kiwifruit have been used with some success to aid tolerance, with the protective effects of the therapy having been shown to persist even after discontinuation of the treatment (Mempel *et al*., 2003; Kerzl *et al*., 2007). A further study by Ukleja-Sokołowska *et al*. (2021) advised a patient with kiwifruit allergy to remove kiwifruit from their diet and support this with starting allergen-specific immunotherapy for grass allergens to support their condition. While specific immunotherapy for emerging allergens, such as kiwifruit, has only currently been used in smaller patient groups, specific immunotherapy for major allergens, such as peanut, milk and egg, has been shown to be effective in supporting the management of these food allergies and as such this treatment should be of continued interest in the management of allergy to both current and emerging food allergens (Gawrońska-Ukleja *et al*., 2013; Muraro *et al*., 2022).

A wide search of the literature was conducted in the current study to identify and capture all available items of evidence that are linked to food allergy and kiwifruit. Out of the total studies that were identified, 107 were suitable for further analysis. Most studies identified were observational studies documenting prevalence of food allergy to kiwifruit and were conducted in Europe, with further research being from North America, Asia, South America, Africa and Oceania. The studies that have been included point towards a variation within the prevalence of food allergy to kiwifruit by location and population, with rates in the researched populations ranging from 0.1%–0.2% (Venkataraman *et al*., 2018) to 100% (Latasa *et al*., 1995) in Europe, 0.35% (Kim *et al*., 2018) to 43.6% (Koga *et al*., 2022) in Asia, 12.2% (Kim & Hussain, 1999) to 17.0% (Beezhold *et al*., 1996) in North America and a study each from Africa and Oceania considering prevalence at 24.1% (Odongo *et al*., 2015) and 0.1–0.5% (Sasaki *et al*., 2018) respectively. In light of these research studies and continued growth within the production of and uses for kiwifruit, the global kiwifruit market is expected to grow by US $2.74 billion from 2022 to 2026 (Reportlinker, 2022), the current work has summarised the information available that relates to the prevalence of food allergy to kiwifruit in the general population globally. It is anticipated that this work will prompt a continued interest in this field and could flag the requirement for further research.

Within the European Union, the United States and many other nations globally, the labelling of all ingredients within food products, including legislated food allergens, is necessitated. The European Union specifies 14 substances or products causing allergies or intolerances within Annex II of 'Council Regulation (EU) No. 1169/2011 on the provision of food information to consumers' (2011), namely, cereals containing gluten (wheat, rye, barley, oats, spelt, kamut or their hybridised strains), crustaceans, eggs, fish, peanuts, soybeans, milk, nuts (almonds (*Amygdalus communis* L.), hazelnuts (*Corylus avellana*), walnuts (*Juglans regia*), cashews (*Anacardium occidentale*), pecan nuts (*Carya illinoinensis* (Wangenh.) K. Koch), Brazil nuts (*Bertholletia excelsa*), pistachio nuts (*Pistacia vera*), macadamia or Queensland nuts (*Macadamia ternifolia*)), celery, mustard, sesame seeds, sulphur dioxide/sulphites at concentrations >10 mg kg^{-1} or 10 mg L^{-1} (Total SO_2), lupin, molluscs and the products of these. Correspondingly, within the United States, nine major food allergens are now outlined being crustacean shellfish, eggs, fish, milk, peanuts, soybeans, tree nuts, wheat and sesame within the Food Allergen Labeling and Consumer Protection Act (FALCPA) (2004) and the Food Allergy Safety, Treatment, Education, and Research (FASTER) Act (2021). At present, kiwifruit, and products thereof, are not recognised as legislated food allergens and do not currently require labelling as such. However, it is of note that as modern dietary trends are including increased consumption of plant-based foods and alternative sources of protein the Food Agricultural Organisation and World Health Organisation, (2022) have had recent interest into emerging food allergens including kiwifruit by categorising them on a watch list for surveillance and ongoing evaluation to be incorporated onto the priority allergen list based on the development of further supporting prevalence, severity and potency evidence. In comparison to other food allergens, kiwifruit allergy has been considered of a similar prevalence to that of fish (codfish), IgE-mediated wheat allergy, soya, sesame and walnut, but of a higher prevalence than celery, buckwheat, mustard, almond, Brazil nut, macadamia, pecan and pine nut (Food Agricultural Organisation and World Health Organisation (2022)). However, allergy to cow's milk, hen's egg and peanut is considered of the highest prevalence and crustaceans, cashew nut,

hazelnut, pistachio and coeliac disease to wheat are of a mixed prevalence, though both of these groups are higher in prevalence than kiwifruit allergy (Food Agricultural Organisation and World Health Organisation (2022)). In terms of kiwifruit allergen severity, there is evidence of anaphylactic reactions within the literature (Blanco *et al.*, 1994; Novembre *et al.*, 1995; Kazemi-Shirazi *et al.*, 2000; Florido Lopez *et al.*, 2002; Mempel *et al.*, 2003; Asero *et al.*, 2007; Palacin *et al.*, 2008a; Bernardi *et al.*, 2010; Popovic *et al.*, 2010; Zhu *et al.*, 2012; Nilsson *et al.*, 2015; Ozturk & Ozyigit, 2015; Tosca *et al.*, 2015; Asaumi *et al.*, 2017; Gabrielli *et al.*, 2021; Ukleja-Sokołowska *et al.*, 2021; D'Amelio *et al.*, 2022) and due to the incorporation of kiwifruit into a range of processed products, could introduce the risk of its consumption as an unintended or unidentified food allergen (Codex Alimentarius, 2020). With regard to the potency of kiwifruit allergens, further research is needed to build a data set to which dose-distribution modelling could be applied (Food Agricultural Organisation and World Health Organisation (2022)).

Considering the increased consumption of kiwifruit, rising prevalence of food allergy to kiwifruit (Eriksson *et al.*, 2004; Lucas *et al.*, 2004; Moreno Álvarez *et al.*, 2015; Osawa *et al.*, 2020; Ruiz Segura *et al.*, 2020; Takemura *et al.*, 2020) and the clinical outcomes, which can be severe, there is a need for clear, accurate and complete food labelling (Choi *et al.*, 2015). The increased use of kiwifruit and focus on repurposing of waste from kiwifruit sources into food products is a logical move by industry, but additional awareness of possible allergenicity to products may be warranted. Whilst improvements in the clarity, consistency and accuracy of precautionary allergen labelling and information for current legislated food allergens have been deemed necessary (Food Standards Agency, 2022), emerging food allergens should also be considered in the discussion. Due to the ongoing expansion within the kiwifruit market, in particular regarding products being targeted at the human food chain, further research is required within this field. Out of the present evidence, multiple research studies have highlighted kiwifruit as a source of a range of allergic reactions, including anaphylaxis, with a widespread global prevalence being of a potential public health interest.

Conclusion

The increases in the production and development of products making use of kiwifruit waste streams from food systems will aid growth to further support sustainable food production systems. The current literature confirms that kiwifruit is highly nutritious, being a beneficial source of many nutrients, which are key to good health. However, the presence of proteins with allergenic properties needs to be recognised, namely, kiwifruit components having cross-reactivity with those responsible for allergy to plant-based foods, pollen and latex. Prevalence of food allergy to kiwifruit has been reported by the current study in a wide population globally, ranging from 0.1%–0.2% to 60.0% in ages 0–18 years and from 0.35% to 38.4% in those aged >18–96 years, with the incidence being shown to be increasing which is possibly due to current dietary trends including greater consumption of plant-based foods like kiwifruit for their nutritional and health benefits. Further research is required in order to better assess the use of emerging raw materials and the repurposing of food waste streams to gain an improved understanding of the associated food safety hazards, such as those containing food allergens, the potential for these commodities to act as allergen vectors or how their introduction may change or increase the food allergen profile of products. This will enable regulators, legislators and industry to establish controls to manage allergenic food safety hazards and further develop precise information in order to protect public health through the clear, consistent and accurate communication of any risks to consumers.

Conflict of interests

The authors declare they have no competing interests.

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Author contributions

Christopher A. James: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Simon Welham:** Supervision (equal); writing – review and editing (equal). **Peter Rose:** Conceptualization (equal); methodology (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal).

Data availability statement

Data sharing is not applicable to this article as all data generated or analysed during this study are included in this published article and its Supporting Information files.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Findings of the reviewed sources addressing the prevalence of food allergy to kiwifruit.

Table S2. Findings of the reviewed clinical trials not considering prevalence of food allergy to kiwifruit.

