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ORIGINAL ARTICLE

Allergens causing occupational asthma: an evidence-based evaluation of the literature

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Abstract
Purpose The aim of this work is to provide an evidence-based evaluation and overview of causative substances in order to improve disease management.
Methods We conducted a database search with MEDLINE via PubMed, screened reference lists of relevant reviews and matched our findings with a list of agents denoted as "may cause sensitisation by inhalation" by the phrase H334 (till 2011 R42). After exclusion of inappropriate publications, quality of the selected studies was rated with the Scottish Intercollegiate Guideline Network (SIGN) grading system. The evidence level for each causative agent was graded using the modified Royal College of General Practitioners (RCGP) three-star system.
Results A total of 865 relevant papers were identified, which covered 372 different causes of allergic work-related asthma. The highest level achieved using the SIGN grading system was 2++ indicating a high-quality study with a very low risk of confounding or bias and a high probability of a causal relationship. According to the modified RCGP three-star grading system, the strongest evidence of association with an individual agent, profession or worksite ("***") was found to be the co-exposure to various laboratory animals. An association with moderate evidence level ("**") was obtained for α-amylase from Aspergillus oryzae, various enzymes from Bacillus subtilis, papain, bakery (flour, amylase, storage mites), western red cedar, latex, psyllium, farming (animals, cereal, hay, straw and storage mites), storage mites, rat, carmine, egg proteins, atlantic salmon, fishmeal, norway lobster, prawn, snow crab, seafood, trout and turbot, reactive dyes, toluene diisocyanates and platinum salts.
Conclusion This work comprises the largest list of occupational agents and worksites causing allergic asthma. For the first time, these agents are assessed in an evidence-based manner. The identified respiratory allergic agents or worksites with at least moderate evidence for causing work-related asthma may help primary care physicians and occupational physicians in diagnostics and management of cases suffering from work-related asthma. Furthermore, this work may possibly provide a major contribution to prevention and may also initiate more detailed investigations for broadening and updating these evidence-based evaluations.

Keywords Occupational asthma · Allergens · Allergology · Diagnostics · Evidence-based grading

Abbreviations

OA	Occupational asthma
RADS	Reactive airways dysfunction syndrome
RCGP	Royal College of General Practitioners
SIGN	Scottish Intercollegiate Guideline Network
WRA	Work-related asthma
LFT	Lung function tests

Xaver Baur and Prudence Bakehe contributed equally to this work.

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sPFT	Serial lung function tests
SIC	Specific inhalation challenge
NSBHR	Non-specific bronchial hyperresponsiveness

Introduction

As shown in various studies, 9–25 % of adult asthma is due to occupational factors (Blanc and Toren 1999; Balmes et al. 2003; Mapp et al. 2005; Toren and Blanc 2009). This asthma group is also known as work-related asthma. It includes occupational asthma, that is, new onset of asthma due to agents in the workplace, and work-aggravated asthma, that is, worsening of pre-existing or concomitant non-occupational asthma by agents in the workplace.

Work-related asthma comprises subtypes of occupational asthma as shown in Fig. 1.

IgE-mediated as well as irritant occupational asthma with not-so-sudden-onset, low-dose-irritant asthma and occupational asthma of unknown pathomechanism all typically showing a latency period from the beginning of causative exposure until appearance of symptoms (Baur et al. 2012b; Burge et al. 2012).

The great majority of occupational asthma cases are based on an IgE-mediated pathomechanism as is the case in adult allergic asthma unrelated to work.

In previous reviews and overviews, up to 300 agents have been reported as causes of occupational asthma (Tarlo and Malo 2009; Tarlo et al. 1998; van Kampen et al. 2000; Sastre et al. 2003; Quirce and Sastre 2011; Malo and Chan-Yeung 2007, 2009; Lombardo and Balmes 2000; Baur 2008; Bernstein et al. 2006).

These causative agents have been classified in two main groups according to their molecular weight: high molecular weight agents and low molecular weight agents. High molecular weight agents typically induce asthma through an IgE-mediated mechanism, while the pathomechanism of many low molecular weight agents is still unknown. Isocyanates and acid anhydrides are examples of the latter group demonstrating allergic as well as irritant effects (Mapp et al. 2005; Bernstein et al. 2006).

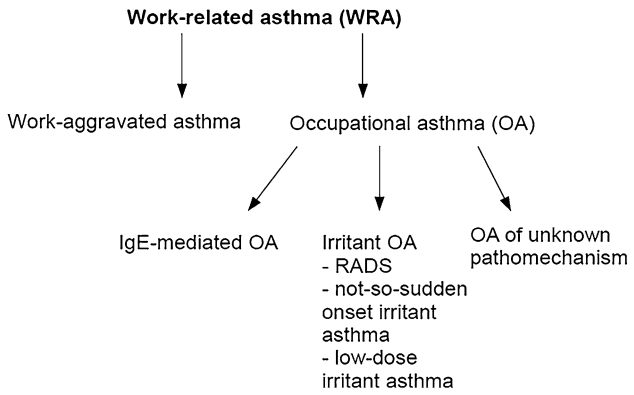

Fig. 1 Subtypes of work-related asthma

New agents are continually being reported as eliciting occupational asthma. Therefore, it is important to constantly keep these lists completed and up-to-date. Furthermore, an evidence-based evaluation of the literature, which does not exist currently, is of particular importance with regard to clinical case management and diagnostics in individual situations. As such, the major aim of this study is to provide an updated evidence-based overview of the present respiratory allergens causing work-related asthma. It should be helpful in clinical practice to identify causes of suspected occupational asthma in the workplace.

In this work, we focused on agents eliciting occupational asthma due to proven IgE-mediated sensitisation. We also included those agents with a likely IgE-mediated pathomechanism, such as platinum salts, that are associated with immediate skin prick test responses but negative results in measurements of specific IgE antibodies. With regard to irritant asthma, a recent publication summarises current knowledge (Baur et al. 2012a).

Methodology

For further methodological details of selection criteria, data extraction and synthesis, quality assessment of individual study and the overall list comprising results of each publication, see online resources.

We conducted a systematic literature search in MEDLINE/PubMed on occupational asthma and its causative agents. The search covered the period from MEDLINE/PubMed's inception until August 2011 and was restricted to publications in English, German or French. The main keywords in the database search were "Bronchial Hyperreactivity", "Airway Obstruction", "Occupational Diseases" and "Occupational Exposure". We also screened the reference lists of already published reviews including their references (van Kampen et al. 2000; Bernstein et al. 2006; Baur 2008; Malo and Chan-Yeung 2009; Tarlo and Malo 2009; Quirce and Sastre 2011). Furthermore, we compared the findings with a list of agents denoted as "may cause sensitisation by inhalation" by the phrase H334 (till 2011 R42) (Baur 2008; ACGIH®; Europäische Gemeinschaft 2001; European Parliament 2008).

Then, we combined results of both the database search and the reviews/summaries. The combination of medical subject headings (MeSH) finally used is the result of an optimised integration of the selection criteria and the comparison with studies found through occupational allergen lists:

("1"[PDAT]: "2011/08/01"[PDAT]) AND ((((((((((("Signs and Symptoms, Respiratory"[Majr] OR "Occupational Diseases"[Majr]) OR "Allergy and Immunology"[Majr]) OR "Respiratory Function Tests"[Majr]) OR "Bronchial Hyperreactivity"[Majr]) OR "Airway Obstruction"[Majr]) OR "Respiratory Hypersensitivity"[Majr]) OR "Lung Diseases, Obstructive"[Majr]) OR "Asthma"[Majr]) OR "Asthma"[Mesh]) OR "Occupational Exposure"[Majr]) AND "ALLERGEN"[Mesh]) AND ("humans"[MeSH Terms] AND (English[lang] OR French[lang] OR German[lang]) AND "adult"[MeSH Terms]).

Studies with non-occupational asthma causes were excluded.

Publications about occupational agents which do not have an IgE-mediated effect on the respiratory tract or with unrelated issues were excluded. We searched for publications reporting studies performed exclusively with human who had been were occupationally exposed to causative agents (see online resources Table A).

The principal study characteristics and study results were systematically extracted using an extraction sheet (see online resources Table B).

We assessed study quality with the help of a check list (see online resources Table C).

After excluding of irrelevant publications (see Table A and Fig. 2), SIGN (Scottish Intercollegiate Guidelines Network) was used to rate the quality of each study (Harbour and Miller 2001). In order to achieve more differentiation among lower evidence grades, we modified the SIGN grading system and added an additional grade (3+; see Table 1). The modified RCGP (Royal College of General Practitioners) three-star system (Newman Taylor et al. 2005) was used to grade the evidence for each agent on basis of all available publications. The system considers quality and quantity of all studies as well as consistency of reported findings. Some modification was necessary for our study. We introduced additional up- and downgrading: [] indicated downgrading due to lower quality of clinical investigations, that is, due to missing objective parameters such as lung function data; further, (*) indicated upgrading from "−" due to at least five reported asthma cases without contradictory findings (see Table 2).

Results

Overview of reported causative allergenic agents

The database search resulted in 1,890 potentially relevant publications (see selection flow diagram, Fig. 2). An additional 475 potentially relevant publications were retrieved from the reference lists of the identified systematic reviews (van Kampen et al. 2000; Malo and Chan-Yeung 2009; Baur 2008; Bernstein et al. 2006; Quirce and Sastre 2011; Tarlo and Malo 2009).

After the exclusion of non-occupational cases, the different search approaches yield a total of 865 relevant studies. These 865 publications refer to 682 partially overlapping individual agents, to 121 "mixed" agents and to 62 worksites reported to cause allergic work-related/occupational asthma. In 41 cases, only the abstract could be read. They were also included and evaluated.

Table 3 presents an overview of the identified agents grouped according to their worksites and professions and their strength of evidence for causing occupational asthma.

Evidence levels in the retrieved literature

Two hundred and thirty-two of the total 865 publications were reviews of cross-sectional studies, case–control studies, cohort studies, longitudinal studies and clinical cross-sectional studies and were rated according to SIGN as 2++ ($n = 2$), 2+ ($n = 18$), 2− ($n = 120$) or 3+ ($n = 92$). The majority of publications represent questionnaire-based surveys, case series and case reports and were rated according to SIGN as 2− ($n = 13$), 3 ($n = 144$) or 3+ ($n = 236$). There was 1 review of cross-sectional studies, 5 case–control studies, 15 cohort studies, 2 longitudinal studies, 209 clinical cross-sectional studies, 54 questionnaire-based surveys, 115 case series and 467 case reports.

The highest level was 2++, indicating a high-quality analytical study (case–control or cohort studies) with a very low risk of confounding, bias or chance and a high probability that the relationship is causal ($n = 2$ studies). Eighteen studies were rated 2+ by SIGN grading of indicating well-conducted analytical studies (case–control or cohort studies) with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal ($n = 17$ studies) and well-conducted systemic reviews of analytical cross-sectional studies ($n = 1$ review). Most of the other analytical studies were rated with a SIGN grade of 2− or 3+ because their design was limited (cross-sectional or longitudinal study) and/or they comprised a high risk of confounding, bias or chance ($n = 212$ studies). Some study designs were difficult to classify, notably surveys, which in many cases had very low analytical evidence, rated 3+ or 3 ($n = 52$ studies). Larger surveys with a lower risk of confounding or bias were graded with 2− ($n = 12$ studies). No study with a SIGN grade of 4 (expert opinion) was identified in this literature search.

Strength of evidence per agent or worksite

The modified RCGP three-star system enables the classification of strength of evidence for the causative role in

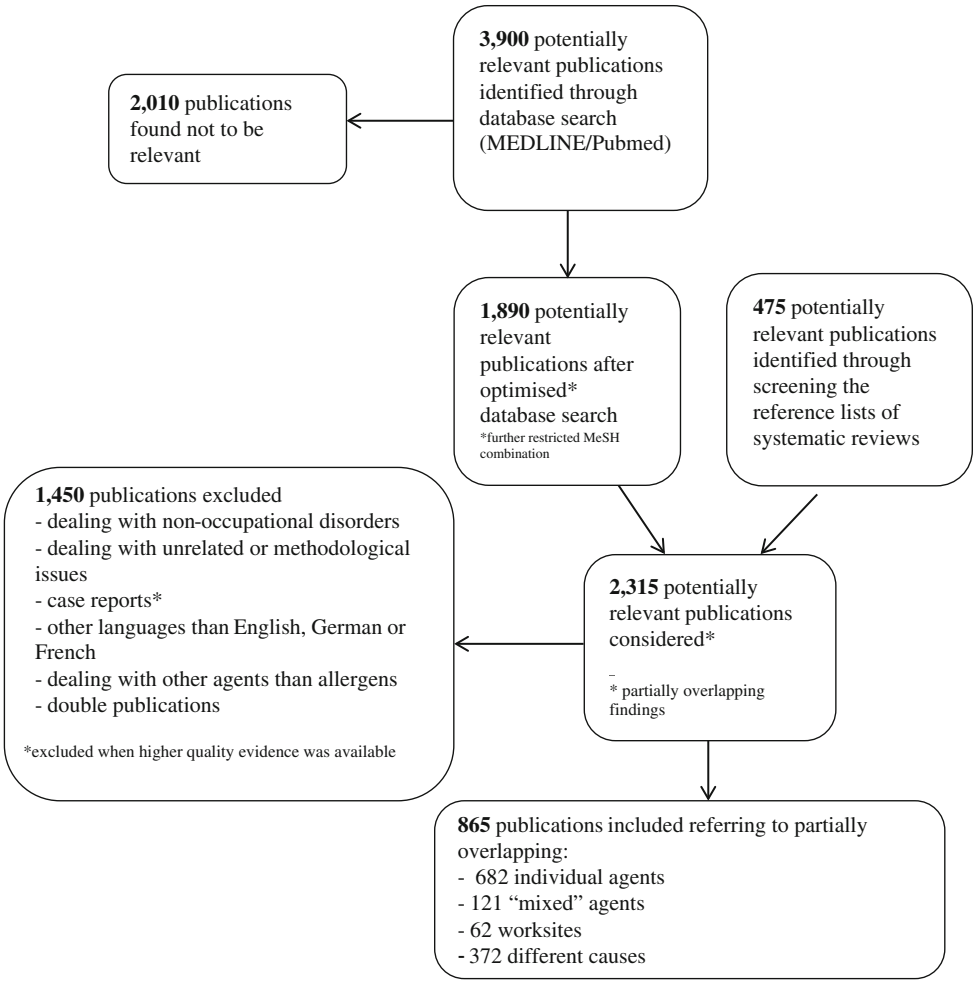

Fig. 2 Flow diagram demonstrating the sources of references

Table 1 The revised Scottish Intercollegiate Guidelines Network (SIGN) grading system (modified)

1++	High-quality meta analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1−	Meta analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies. High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal. Well-conducted systematic reviews of analytical cross-sectional studies
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal. Well-conducted analytical cross-sectional or longitudinal studies with low risk of confounding, bias or chance.
3+	Cross-sectional, longitudinal studies or Surveys with high risk of confounding, bias or chance and a significant risk that the relationship is not causal, non-analytical studies with $n \geq 5$ cases
3	Non-analytic studies, for example, case reports, case series
4	Expert opinion

allergic occupational asthma of each reviewed agent. The strongest evidence obtained was three stars "***" for one worksite, that is, exposure to various laboratory animals, indicating a strong strength of evidence provided by generally consistent findings in multiple, high-quality scientific studies. For 18 agents or worksites, strength of evidence corresponded to two stars "**" indicating moderate evidence (Table 2). For nine of them, this level was based on high-quality case–control or cohort studies (SIGN 2++) as well as well-conducted studies with a low risk of confounding or bias (SIGN 2+). For nine of these 18 agents, SIGN levels of individual studies were lower (SIGN 2−).

Table 2 The modified Royal College of General Practitioners (RCGP) three-star system of the British Occupational Health Research Foundation (Nicholson et al. 2010)

***	Strong evidence—provided by generally consistent findings in multiple, high-quality scientific studies
**	Moderate evidence—provided by generally consistent findings in fewer, smaller or lower quality scientific studies
*[*]	Moderate evidence—provided by generally consistent findings in fewer, smaller or lower quality scientific studies, based on questionnaire-conducted studies or other weak evidence (clinical weakness (absence of LFT, sPFT, SIC))
*	Limited or contradictory evidence—provided by one scientific study (analytic) or inconsistent findings in multiple scientific studies
[*]	Limited or contradictory evidence—provided by one scientific study based on questionnaires or other weak evidence (clinical weakness (absence of LFT, sPFT, SIC))
(*)	Very limited or contradictory evidence—provided by at least three case reports, one case series, one non-analytic study or one occupational disease statistic study with at least five asthma cases
–	No scientific evidence—based on clinical studies, theoretical considerations and/or clinical consensus

Moderate evidence, provided by generally consistent findings in fewer, smaller or lower quality scientific studies with clinical weakness ("*[*]"), was found for 17 agents.

Limited or contradictory evidence, provided by only one scientific study or inconsistent findings in multiple scientific studies ("*"), was identified for 18 agents. We downgraded ("[*]") the evidence for 24 agents due to missing objective data.

The majority of agents were reported in non-analytical studies. Therefore, in the case of many agents, no scientific evidence could be obtained. An upgrading ["(*)"] could be realised if at least five cases were identified by case reports or case series proving allergic occupational asthma. Thus, the strength of evidence ranged from very limited or contradictory evidence ["(*)"] for 19 agents to no scientific evidence "–" for 275 agents, worksites or professions (Table 4).

Diagnostic aspects and allergic OA as outcome

In the retrieved publications, different procedures were used for the diagnosis of occupational asthma, with specific inhalation challenge (SIC) and serial lung function tests (sPFT) being considered the most reliable diagnostic tools (Leroyer et al. 1998; Ortega et al. 2002; Banks 2003; Tan and Spector 2003; Moscato et al. 1995).

SIC was used to confirm occupational asthma in 444 of 865 studies (51.3 %). SIC was only applied in non-analytical studies. sPFT were identified in 186 of included studies (21.5 %).

Lung function testing (LFT) was another frequent ($n = 438$; 50.6 %) diagnostic method for occupational asthma showing an obstructive ventilation pattern.

Exclusively, self-reported asthma symptoms or physician-reported asthma as documented in questionnaires as an alternative diagnostic approach for occupational asthma (Bernstein et al. 2006; Malo et al. 1991) was applied in 291 studies (33.6 %) [no LFT, non-specific bronchial hyperresponsiveness (NSBHR) or sPFT].

Another seven studies (0.8 %) did not have clear diagnosed occupational asthma but reported obstructive ventilation pattern in LFT.

In order to confirm allergic occupational asthma, it is necessary to document immediate-type sensitisation.

In several studies, this was accomplished solely with the skin prick test (SPT; $n = 672$; 77.7 %). In other studies, specific IgE tests were used in addition (spec. IgE, $n = 518$; 59.8 %).

Allergic occupational asthma could be diagnosed with these tools in many cases.

We identified 664 studies demonstrating immediate-type sensitisation to occupational agents by means of SPT and/or specific IgE tests. Considering our evaluation criteria, the most frequent occupational asthma causes were wood dust from western red cedar (448 cases), proteases and alcalases from *Bacillus subtilis* (279 cases), laboratory animals (229 cases), spider mites (174 cases), bakery (174 cases), latex (136 cases), various tea dusts (134 cases), storage mites (130 cases), papain (109 cases) and platinum salts (96 cases).

There were also several agents where these diagnostic methods were not applied or did not confirm the suspicion of allergic work-related asthma even if occupational asthma was highly probable.

Discussion

The aim of this study was to provide an evidence-based and practically relevant overview of the respiratory allergenic agents, worksites and professions causing occupational asthma. In addition to optimised diagnostic tools and adequate management strategies, prevention of occupational asthma is a great challenge for healthcare systems today. An all-embracing list of causative agents as aspired to in this work may be an essential part of respective management strategies. It could help in diagnostics, as well as in the control and reduction of exposures to harmful

Table 3 Taxonomical classification of the agents and strength of evidence for allergic occupational asthma as reported by the retrieved literature

Taxonomical classification of agents	Strength of evidence per agent (three-star system of RCGP[a])	Total no. of allergic asthma cases per agent, *n*—specific sensitization is not confirmed	References[b]
Animals (*Animalia*)			
Arthropoda			
Arachnids (Arachnida)			
Mites (Acarina)			
Predatory mites (Phytoseiidae)	*[*]	35	Groenewoud et al. (2002), Skousgaard et al. (2010), Kronqvist et al. (2005), Johansson et al. (2003)
Spider mites (Tetranychidae)	*[*]	174	Astarita et al. (2001), Kim et al. (1999), Navarro et al. (2000), Jeebhay et al. (2007), Kim et al. (1999), Park et al. (2000), Burches et al. (1996), Astarita et al. (1994), Delgado et al. (1997), Kim et al. (1999), Ashida et al. (1995, ABSTRACT), Kroidl et al. (1992), Carbonnelle et al. (1986), Michel et al. (1977), Delgado et al. (1994), Cisteró-Bahima et al. (2000), Erlam et al. (1996, Abstract)
Storage mites (Acaridae, Glycyphagidae)	**	130	Kronqvist et al. (1999), Hage-Hamsten van et al. (1985), Hage-Hamsten van et al. (1987), Cuthbert et al. (1984), Blainey et al. (1989), Patussi et al. (1994, Abstract), Revsbech and Andersen (1987), Blainey et al. (1988), Müsken et al. (2000, Abstract), Cuthbert et al. (1979), Koistinen et al. (2006), Armentia et al. (1992), Revsbech and Dueholm (1990), van Hage-Hamsten, Ihre et al. (1988), Iversen et al. (1992, Abstract), Armentia et al. (1994, Abstract), Warren et al. (1983), Alvarez et al. (1999), (Garces) Sotillos et al. (1991), Vieluf et al. (1993)
Poultry mites (Macronyssidae)	(*)	12	Bar-Sela et al. (1984)
House dust mites (*Dermatophagoides pteronyssinus and Dermatophagoides farinae*)	[*]	14	Rimac et al. (2009), Brunetto et al. (2009), Menzies et al. (1997)
Insects (insecta)			
Australia sheep blowfly (*Lucilia cuprina*)	–	1	Kaufman et al. (1989), Kaufman et al. (1986)
Bee moth larvae (*Galleria mellonella*), wax worm, wax moth	–	1	Stevenson and Mathews (1967)
Caddis fly (*Hydropsyche recurvata*)	–	1	Kraut et al. (1994)
Champignon flies (family: Phoridae and Sciaridae)	–	1	Cimarra et al. (1999)
Cockroach (*Blaberus giganteus*)	–	1	Marraccini et al. (2007, Abstract), Kanerva et al. (1995), Steinberg et al. (1987)
Common housefly (*Musca domestica*)	–	1	Focke et al. (2003), Tee et al. (1985)
Confused flour beetle (*Tribolium confusum*)	–	1	Alanko et al. (2000)
Cricket (*Acheta domestica*)	–	4	Bagenstose et al. (1980), Linares et al. (2008), Bartra et al. (2008)
Dermestidae spp. beetle	–	2	Brito et al. (2002), Sheldon and Johnston (1941)
Flour moth (*Ephestia kuehniella*)	[*]	8	Mäkinen-Kiljunen et al. (2001), Armentia et al. (2004)

Table 3 continued

Taxonomical classification of agents	Strength of evidence per agent (three-star system of RCGP[a])	Total no. of allergic asthma cases per agent, *n*—specific sensitization is not confirmed	References[b]
Fruit fly (*Drosophila melanogaster*)	–	3	Spieksma et al. (1986)
Grain weevil (*Sitophilus granarius*)	–	–	Rosenau et al. (1993)
Grasshopper (*Melanoplus sanguinipes*)	–	4	Soparkar et al. (1993)
Ground bugs (family Lygaeidae: *Metopoplax ditomoides* et *Microplax albofasciato*)	–	1	Lázaro et al. (1997)
Gypsy moth caterpillar (*Lymantria dispar*)	–	2	Etkind et al. (1982)
Herring worm (*Anisakis simplex*)	–	3	Armentia et al. (1998), Scala et al. (2001)
Honeybee (*Apis mellifera*)	–	1	Ostrom et al. (1986)
Lentil pest (*Bruchus lentis*)	–	1	Armentia et al. (2003)
Lesser mealworm (*Alphitobius diaperinus*)	–	2	Schroeckenstein et al. (1988)
Live fish bait	*	16	Siracusa et al. (2003), Siracusa et al. (1994), Stevenson et al. (1967)
Locust (*Schistocerca gregaria* and *Locusta migratoria*), cicada	*[*]	19	Burge et al. (1980), Tee et al. (1988), Lopata et al. (2005)
Mealworm (larva of beetle *Tenebrio molitor*)	(*)	5	Bernstein et al. (1983), Rudolph et al. (1979), Friedrich (1986), Schroeckenstein et al. (1990)
Mexican bean weevil (*Zabrotes subfasciatus* boh.)	–	2	Wittich (1940)
Mosquito larvae (*Echinodorus plamosus*)	–	1	Resta et al. (1982)
Non-biting midges (*Chironomus thummi thummi*)	*	34	Liebers et al. (1993)
Screwworm fly (*Cochliomyia hominivorax*)	[*]	10	Gibbons et al. (1965)
Sewer fly (*Psychoda alternata*)	–	1	Gold et al. (1985)
Silkworm, silk, sericin	*[*]	35	Harindranath et al. (1985), Uragoda and Wijekoon (1991), Charpin and Blanc (1967)
Water-flea (Daphnia)	–	2	Meister (1978)
Various insects	–	34	Lugo et al. (1994), Armentia et al. (1997)
Crustaceans (Crustacea)			
Lobster (Family Nephropidae)	–	2	Lemière et al. (1996), Patel and Cockcroft (1992)
Prawn (*Nephrops norwegicus*), Norway lobster	**	22	McSharry et al. (1994), Gaddie et al. (1980)
Shrimp (Order Decapoda)	[*]	5	Desjardins et al. (1995), Lemière et al. (1996), Goetz et al. (2000), Baur et al. (2000), Carino et al. (1985)
Snow crab (*Chinoecetes opilis*)	**	30	Ortega et al. (2001), Cartier et al. (1984)
Molluscs (Mollusca)			
Clam (Class Bivalvia)	–	2	Desjardins Malo et al. (1995)
Cuttle-fish (*Sepia apama*)	–	1	Tomaszunas et al. (1988), Beltrami et al. (1989)
Green-lipped mussel (*Perna canaliculus*)	–	–	Glass et al. (1998)
Scallop (Family Pectinidae)	–	1	Goetz et al. (2000)
Octopus (Order Octopoda)	–	1	Rosado et al. (2009)
Sponges (Porifera)			
Marine sponge, powdered (*Dysidea herbacea*)	–	1	Baldo et al. (1982)

Table 3 continued

Taxonomical classification of agents	Strength of evidence per agent (three-star system of RCGP[a])	Total no. of allergic asthma cases per agent, *n*—specific sensitization is not confirmed	References[b]
Cnidaria			
Red soft corals (*Dendronephthytia nipponica*)	[*]	9	Onizuka et al. (1990, Abstract)
Spinal cords (chordata), vertebrata			
Fishes			
Atlantic Salmon (*Salmo salar*), Seafood, Fishmeal, Trout, Turbot (*Scophthalmus maximus*),	**	28	Shiryaeva et al. (2010), Douglas et al. (1995), Jeebhay et al. (2000), Droszcz et al. (1981), Sherson et al. (1989), Pérez Carral et al. (2010), Rodríguez et al. (1997)
Birds (Aves)			
Budgerigar (*Melopsittacus undulatus*)	[*]	5	Faux et al. (1971), Toorenenbergen van et al. (1985)
Canary (*Serinus canaria*)	–	–	Toorenenbergen van et al. (1985)
Various birds	[*]	17	Krakowiak et al. (2002), Hargreave and Pepys (1972), Tauer-Reich et al. (1994), Hoffman and Guenther (1988), Świderska-Kielbik et al. (2009)
Poultry	[*]	18	Radon et al. (2001), Kimbell-Dunn et al. (1999), Bar-Sela et al. (1984)
Amphibians (Amphibia)			
Bull frog (*Rana catesbieana*)	–	2	Nakazawa et al. (1983)
Frog (*Rana esculenta*)			Armentia et al. (1988)
Mammals (Mammalia)			
Black bat (*Tandarida major*)	(*)	9	El-Ansary et al. (1987), Senti et al. (2000), Spiewak et al. (1996)
Cow (*Bos primigenius taurus*)	*[*]	84	Walusiak et al. (2004), Terho et al. (1987), Terho et al. (1985), Hinze and Bergmann (1995), Ylönen et al. (1992), Virtanen et al. (1988)
Deer (*Cervus elaphus, Capreolus capreolus*)	–	1	Gillespie et al. (1985), Nahm et al. (1996), Carballada et al. (2006)
Elk (*Cervus canadensis*)	–	–	Gillespie et al. (1985)
Gerbil (*Meriones unguiculatus*)	–	1	De las Heras et al. (2010)
Guinea pig (*Cavia porcellus*)	–	3	Hanada et al. (1995)
Horse (*Equus ferus*)	–	–	Tutluoglu et al. (2002)
Mink (*Mustela vison*)	–	1	Jimenez Gomez et al. (1996)
Monkey (Infraorder Simiiformes)	–	2	Petry et al. (1985)
Mouse (*Mus musculus*)	[*]	8	Schumacher et al. (1981), Newman Taylor et al. (1977), Muñoz et al. (2007)
Pig farming	–	4	Radon et al. (2000), Labrecque et al. (2004), Dosman et al. (2004/2006), Harries and Cromwell (1982), Brennan (1985)
Reindeer (*Rangifer tarandus*)	–	1	Reijula et al. (1991)
Rat (*Rattus norvegicus*)	**	89	Cullinan et al. (1999), Nieuwenhuijsen et al. (2003), Hollander et al. (1997), Cullinan et al. (1994), Hollander et al. (1998), Platts-Mills et al. (1987), Lieutier-Colas et al. (2002), Davies et al. (1983), Newman Taylor et al. (1977)
Sheep (*Ovis aries*)	–	–	Radon and Winter (2003)
Animal products			

Table 3 continued

Taxonomical classification of agents	Strength of evidence per agent (three-star system of RCGP[a])	Total no. of allergic asthma cases per agent, *n*—specific sensitization is not confirmed	References[b]
Beef, raw (*Bos primigenius*)	–	1	San-Juan et al. (2005)
Bovine serum albumin (BSA) powder (*Bos primigenius*)	–	–	Joliat and Weber (1991)
Clam's liver (*Bivalve molluscs*)	–	1	Karlin (1979)
Endocrine glands (ovaries, testes, pancreas, adrenal glands) of bovine origin	–	1	Breton et al. (1989)
Honey (Bees, Family Hymenoptera)	–	1	Johnson et al. (1999)
Ivory (*Loxadonta africana*)	–	–	Armstrong et al. (1988)
Shark cartilage (Order Selachimorpha)	–	1	Ortega et al. (2002)
Milk proteins (*Bos taurus*)	–	4	Sripaiboonkij et al. (2008), Bernaola et al. (1994), Olaguibel et al. (1990), Rossi et al. (1994), Vargiu et al. (1994)
Egg proteins (*Gallus gallus*)	**	36	Smith et al. (1990), Smith et al. (1987), Bernstein et al. (1987), Edwards et al. (1983), Leser et al. (2001, Abstract), Escudero et al. (2003), Valero et al. (1996), Blanco Carmona et al. (1992), Bernstein et al. (1993), Anibarro Bausela and Fontela (1996)
Plants (Plantae)			
Family Amaranthaceae			
Brazil ginseng root (*Pfaffia paniculata*)	–	1	Subiza et al. (1991)
Family Apiacea = Umbelliferae			
Bishop's weed (*Ammi majus*), Queen Anne's lace	–	1	Kiistala et al. (1999)
Carrot (*Daucus carota*)	–	3	Quirce et al. (1997), Moreno-Ancillo et al. (2005)
Coriander (*Coriandrum sativum*)	–	1	Sastre et al. (1996)
Fennel seed (*Foeniculum vulgare*)	–	1	Schwartz et al. (1997)
Family Araceae			
Banha (*Pinellia ternata*)	–	1	Park et al. (1994)
Canari palm pollen (*Phoenix canariensis*)	–	1	Blanco et al. (1995)
Spathe flower (*Spathiphyllum wallisii*)	–	1	Kanerva et al. (1995)
Family Araliaceae			
Umbrella tree (*Schefflera*)	–	1	Grob et al. (1998)
Family Asclepiadaceae			
Madagascar jasmine (*Stephanotis floribunda*)	[*]	4	Zee van der et al. (1999)
Family Bombacaceae			
Kapok (*Ceiba pentandra Gaertner*)	–	–	Kern und Kohn (1994)
Family Brassicaceae (Cruciferae)			
Arabidopsis thaliana	–	1	Yates et al. (2008)
Cabbage	–	1	Quirce et al. (2005)
Cauliflower (*Brassica oleracea* var. Botrytis)	–	1	Quirce et al. (2005), Hermanides et al. (2006)
Oilseed rape flour	–	3	Alvarez et al. (2001), Suh et al. (1998)
White wall rocket pollen (*Diplotaxis erucoides*)	–	1	Brito et al. (2001), Garcia-Ortega et al. (2001)
White mustard (*Sinapis alba*)	–	–	Anguita et al. (2007)

Table 3 continued

Taxonomical classification of agents	Strength of evidence per agent (three-star system of RCGP[a])	Total no. of allergic asthma cases per agent, *n*—specific sensitization is not confirmed	References[b]
Family Cactacea			
Carnation (*Dianthus caryophyllus*)	–	1	Paulsen et al. (1997)
Carnation (*Dianthus caryophyllus*)	(*)	15	Sanchez-Guerrero et al. (1999), Cisteró-Bahima et al. (2000), Sáncher-Fernández et al. (2004), Vidal and Polo (1998)
Family Cannabaceae			
Hops (*Humulus lupulus*)	–	1	Newmark (1978)
Family Caryophyllaceae			
Baby's breath (*Gypsophila paniculata*)	–	3	Antépara et al. (1994), Schroeckenstein et al. (1990), Twiggs et al. (1982), Vidal and Polo (1998)
Family Chenopodiaceae			
Swiss chard (*Beta vulgaris* L. *cycla*)	–	2	Parra et al. (1993), Hoz de la et al. (1991)
Family Compositae = Asteraceae			
Artichoke, globe (*Cynara scolymus*)	–	3	Miralles et al. (2003), Quirce et al. (1996)
Camomile (*Matricaria chamomilla*)	–	1	Rudzki et al. (2003)
Chicory (*Cichorium intybus*)	–	4	Cadot et al. (1996), Nemery and Demedts (1989), Escudero et al. (1999), Pirson et al. (2009)
Chrysanthemum (*Chrysanthemum*)	[*]	9	Groenewoud et al. (2002), Piirilä et al. (1994)
Flowers	*	6	Akpinar-Elci et al. (2004), Uter et al. (2001, Abstract)
Lettuce (*Lactuca sativa*)	–	1	Escudero et al. (1999)
Marigold flour (*Tagetes erecta, Calendula officinalis*)	–	1	Lluch-Perez et al. (2009)
Milk thistle (*Silybum marianum*)	–	1	Bircher and Wütrich (1992)
Safflower (*Carthamus tinctorius*)	–	1	Compes et al. (2006)
Sunflower pollen (*Helianthus annuus*)	*	3	Atis et al. (2002), Jiménez et al. (1994), Bousquet et al. (1985)
Sunflower seeds (*Helianthus annuus*)	–	1	Vandenplas et al. (1998)
Yarrow (*Achillea millefolium*)	–	1	Compes et al. (2006)
Family Cucurbitaceae			
Courgette (*Cucurbita pepo*)	–	1	Miralles et al. (2000)
Family Euphorbiaceae			
Castor beans (*Ricinus communis*)	[*]	16	Topping et al. (1982), Patussi et al. (1990, Abstract), Panzani et al. (1986), Davison et al. (1983), Baur et al. (1998), Merget et al. (1994)
Copperleaf (*Acalypha wilkesiana*)	–	1	Perez et al. (2006)
Latex (*Hevea brasiliensis*)	**	136	Bousquet et al. (2006), Archambault et al. (2001), Liss et al. (1997), Chaiear et al. (2001), Grzybowski et al. (1996), Carrillo et al. (1995), Hunt et al. (1995), Vandenplas et al. (1995), Tarlo et al. (1997), Baur et al. (1995), Tarlo et al. (1990), Zuskin et al. (1998), Vandenplas et al. (2001), Baur et al. (1992), Jäger et al. (1992), Orfan et al. (1994), Anibarro et al. (2010)
Plukenetia volubilis seeds	–	1	Bueso et al. (2010)

Table 3 continued

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Family Iridaceae			
Freesia (*Freesia hybride*)	–	1	Toorenenbergen van and Dieges (1984), Piirilä et al. (1994)
Saffron pollen (*Crocus sativus*)	–	1	Feo et al. (1997)
Family Lamiaceae			
Bells of Ireland, pollen of (*Molucella laevis*)	–	1	Miesen et al. (2003)
Family Leguminosae			
Acacia (*Gum arabic*)	–	–	Fowler (1952)
Carob bean flour (*Ceratonia siliqua*)	–	3	Brempt van der et al. (1992), Scoditti et al. (1996), Bircher and Wütrich (1992)
Chick pea (*Cicer arietinum*)	–	1	Martin et al. (1992)
Chickling vetch (*Lathyrus sativus*)	–	1	Valdivieso et al. (1988)
Green bean (*Phaseolus multiflorus*)	–	2	Igea et al. (1994), Parra et al. (1993)
Guar gum (*Cypamopsis tetragonolobus*)	*	6	Malo et al. (1990), Lagier et al. (1990)
Gum arabic (*Acacia senegal*)	(*)	11	Bohner et al. (1941), Sander et al. (2006)
Henna, black (*Indigofera argentea*)	–	1	Scibilia et al. (1997)
Lathyrus sativus flour	–	2	León et al. (2001), Gironés et al. (2005)
Lentil (*Lens culinaris*)	–	1	Martin et al. (1992)
Liquorice roots, licorice (*Glycyrrhiza glabra*)	–	1	Cartier et al. (2002)
Mimosa (*Acacia floribunda*)	–	4	Ariano et al. (1991)
Pea, perennial (*Lathyrus odoratus*), sweetpea, flour	–	2	Jansen et al. (1995), Bhagat et al. (1995)
Senna (*Cassia senna*)	*	6	Marks et al. (1991), Steger et al. (2000), Helin and Mäkinen-Kiljunen (1996), Baur and Luderschmidt (1983)
Vetch (*Vicia sativa*)	–	1	Picón et al. (1991)
Family Liliaceae			
Amaryllis (*Amaryllis hippeastrum*), hybrid cultivate of hippeastrum	–	1	Jansen et al. (1996)
Asparagus (*Asparagus officinalis*)	(*)	10	Tabar et al. (2004), Eng et al. (1996), Lopez-Rubio et al. (1998)
Daffodil (*Narcissus pseudonarcissus*), Trumpet narcissus	–	1	Gonçalo et al. (1987)
Easter Lily (*Lilium longiflorum*)	–	2	Piirilä et al. (1999), Lahti (1986), Vidal and Polo (1998)
Garlic dust (*Allium sativum*)	(*)	10	Añíbarro et al. (1997), Seuri et al. (1993), Lybarger et al. (1982), Falleroni et al. (1981)
Hyacinth (*Hyacinthus orientalis*)	–	–	Piirilä et al. (1998)
Onion (*Allium cepa*)	–	2	Valdivieso et al. (1994), Navarro et al. (1995)
Sarsaparilla root dust (*Smilax regelii*)	–	1	Vandenplas et al. (1996)
Tulip (*Tulipa*)	–	4	Piirilä et al. (1994), Krüsmann and Hausen (1987), Lahti (1986)
Sanyak (*Dioscorea batatas*)	–	1	Park et al. (1994)
Spice dust: Garlic (*Allium sativum*), Onion (*Allium cepa*)	–	2	Van der Walt et al. (2010)

Table 3 continued

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Family Lythraceae			
Henna (*roots of Lawsonia inermis*)	–	4	Starr et al. (1982), Frosch and Hausen (1986), Pepys et al. (1976), Majoie et al. (1996, Abstract)
Family Moraceae			
Weeping fig (*Ficus benjamina*)	*	10	Axelsson et al. (1987), Axelsson et al. (1985), Grob et al. (1998), Diez-Gomez et al. (1998)
Family Myristicaceae			
Mace (*Myristicia fragans*)	–	1	Sastre et al. (1996)
Family Myrsinaceae			
Cyclamen pollen (Genus Cyclamen)	–	1	Bolhaar and van Ginkel (2000)
Familiy Oleaceae			
Olive fruit (*Olea*)	–	1	Palomares et al. (2008)
Family Papaveraceae			
Poppy (*Papaver somniferum*)	*	6	Moneo et al. (1993)
Family Passifloraceae			
Passion flower *leaves* (*Passiflora alata*), maracuja	–	1	Giavina-Bianchi et al. (1997)
Family Pedaliaceae			
Sesame seeds (*Sesame indicum*)	–	1	Alday et al. (1996), Keskinen et al. (1991
Family Plantaginaceae			
Senna and Ispaghula husks	*	4	Marks et al. (1991)
Psyllium (*Plantago ovata, Plantago psyllium or Plantago indica*)	**	31	Nelson (1987), Malo et al. (1990), Kirby et al. (1986), Bardy et al. (1987), McConnochie et al. (1990), Göransson and Michaelson (1975), Machado et al. (1983), Cartier et al. (1987), Busse and Schoenwetter (1975), Vaswani et al. (1996), Gauss et al. (1985)
Family Plumbaginaceae			
Statice (*Limonium tataricum*), sea lavender	–	1	Ueda et al. (1992), Quirce et al. (1993)
Family Poaceae = Gramineae			
Esparto grass (*Stipa tenacissima*)	–	1	Ruiz-Hornillos et al. (2007, Abstract)
Grass juice (*Lolium perenne*)	–	1	Subiza et al. (1995)
Rice (*Oryza sativa*)	–	3	Kim et al. (2010)
Family Rosacea			
Peach (*Prunus persica*)	–	2	Moya et al. (2002), García et al. (2004)
Raspberry (*Rubus idaeus*)	–	1	Sherson et al. (2003)
Rose (*Rosa rugosa*)	*	20	Demir et al. (2002), Kwaselow et al. (1990), Akkaya et al. (2004)
Strawberry (*Fragaria ananassa*)	–	1	Patiwael et al. (2010)
Family Rubiaceae			

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Taxonomical classification of agents	Strength of evidence per agent (three-star system of RCGP[a])	Total no. of allergic asthma cases per agent, *n*—specific sensitization is not confirmed	References[b]
Coffee: raw (*Coffea arabica*), Green coffee, Castor beans, roasted coffee	*[*]	51	Jones et al. (1982), Thomas et al. (1991), Romano et al. (1995), Larese et al. (1998), Žuškin et al. (1981), Zuskin et al. (1979), Osterman et al. (1985), Zuskin et al. (1985), Karr et al. (1978), Karr (1979), Wallenstein and Schöneich (1983), Lemiere et al. (1996), Müsken et al. (1992), Herrmann et al. (1991)
Ipecacuanha (*Cephaelis ipecacuanha* and/or *Cephaelis acuminata*)	–	–	Luczynska et al. (1984)
Family Solanaceae			
Eggplant pollen (*Solanum melongena*)	–	1	Gil et al. (2002)
Paprika (*Capsicum annuum*)	*[*]	55	Patiwael et al. (2009), Groenewoud et al. (2002), Toorenenbergen van and Dieges (1984), Sastre et al. (1996), Toorenenbergen van and Dieges (1985)
Potato (*Solanum tuberosum*)	–	2	Zock et al. (1996), Quirce et al. (1989)
Tobacco (*Nicotiana tabacum*)	*[*]	2	Mustajbegovic et al. (2003), Valic et al. (1976), Viegi et al. (1986), Mukhtar et al. (1991), Uitti et al. (1998), Kjaergaard et al. (1989), Lander and Gravesen (1988), Gleich et al. (1980), Baur (1993)
Family Sterculiaceae			
Cacao beans (*Theobroma cacao*)	–	1	Perfetti et al. (1997)
Family Theaceae			
Tea dust, various species	*[*]	8	Zuskin and Skuric (1984), Zuskin et al. (1985), Hill and Waldron (1996), Uragoda (1980), Jayawardana and Udupihille (1997), Cartier and Malo (1990), Shirai et al. (1994), Lewis and Morgan (1989), Senff et al. (1989), Uragoda (1970), Roberts and Thomson (1988)
Other plant families			
Dried fruits and teas	–	–	Zuskin et al. (1996)
Flowers	[*]	10	Jong de et al. (1998), Goldberg et al. (1998)
Herbal tea (containing chaparral, red clover, mint etc.)		–	Blanc et al. (1986)
Herbal tea	–	–	Castellan et al. (1981)
Herbs, aromatic (thyme, rosemary, bay leaf, garlic)	–	1	Lemière et al. (1996)
Lime flower	–	1	Rudzki et al. (2003)
Natural fibres, not specified	–	4	Muittari et al. (1978)
Pectin (carbohydrate of plant cells)	–	2	Cohen et al. (1993), Kraut et al. (1992)
Sisal	–	2	Zuskin et al. (1994)
Spices: Coriander (*Coriandrum sativum*) and other spices: mace (*Myristica fragrans*), ginger (*Zingiber officinale*), paprika (*Capsicum tetragonum*), curry.	–	1	Toorenenbergen van and Dieges (1985)
Tragacanth gum	–	1	Bircher and Wütrich (1992)
Voacanga africana seed dust (family Apocynaceae)	–	1	Hinojosa et al. (1987)
Natural thickening products	–	3	Steger et al. (2000)

Table 3 continued

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Wood dust			
Maple (hardwood) and pine (softwood)	–	–	Whitehead et al. (1981, Abstract)
East African teak trees	–	–	Rongo et al. (2002)
Wood dust, not specified	–	–	Paggiaro et al. (1986, ABSTRACT)
Wood (Eucalypt, radiata pine, meranti, sugar pine, tasmanian oak, american oak, jarrah, tasmanian blackwood, wester red cedar)	–	–	Mandryk et al. (1999)
Various (Abies, Chestnut, Douglas, Framire, Mansonia, Oak, Obeche, Walnut, White poplar)	*	9	Carosso et al. (1987)
Wood dust (not specified)	–	–	Holness et al. (1985)
Various woods	(*)	11	Oertmann and Bergmann (1993), Kersten and von Wahl (1994), Fasani et al. (1982, Abstract), Aguwa et al. (2007)
Exotic woods	–	–	Colas et al. (1985, Abstract)
Rimu (*Dacrydium cupressium*) and other wood dust Kauri (*Agathis australis*), Tawa (*Beilschmedia tawa*) etc.	–	–	Norrish et al. (1992)
Hardwood			
Family Bignoniaceae			
Ipe, Brazilian walnut (*Tabebuia* spp.)	–	2	Algranti et al. (2005), Yacoub et al. (2005)
Family Ebenaceae			
Ebony wood (*Diospyros crassiflora*)	–	–	Maestrelli et al. (1987), Kopferschmitt-Kubler et al. (1992, Abstract)
Family Fagaceae			
Beech (*Fagus silvatica*)	–	–	Spiewak et al. (1994)
Cabreuva (*Myrocarpus frondosus*)	–	1	Pala et al. (2010)
Oak (*Quercus robur*)	–	–	Malo et al. (1995), Sosman et al. (1969), Spiewak et al. (1994)
Family Juglandaceae			
Central American walnut (*Juglans olanchana*)	–	–	Bush and Clayton (1983)
Family Lauraceae			
Imbuia (*Phoebe porosa*), Brazilian Walnut	–	1	Jeebhay et al. (1996)
Family Leguminosae			
African Zebrawood (*Microberlinia*)	–	1	Bush et al. (1978)
Angelim pedra (*Hymenolobium petraeum*)	–	1	Alday et al. (2005)
Blackwood (*Acacia melanoxylon*)	–	–	Wood-Baker and Markos (1997)
Cabrueva (*Myrocarpus fastigiatus*)	–	–	Innocenti et al. (1991)
Cedorana (*Cedrelinga catenaeformis*)	–	1	Alvarez Eire et al. (2006)
Cocabolla (*Dalbergia retusa*)	–	1	Eaton (1973)
Fernambouc (*Caesalpina echinata* or *Guilandia echinata*)	–	1	Hausen and Herrmann (1990)
Jatoba wood (*Hymenaea courbaril*)	–	–	Quirce et al. (2004)
Kejaat (*Pterocarpus angolensis*)	–	1	Ordman (1949)
Locust wood (*Robinia pseudoacacia*)	–	2	Kespohl et al. (2006)

Table 3 continued

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Palisander, Brazilian rosewood (*Dalbergia nigra*)	–	1	Godnic-Cvar and Gomzi (1990)
Tali wood (*Erythrophleum suaveolens*), elondo, missanda, muave	–	–	Quirce et al. (2004)
Family Meliaceae			
Mahogany	–	–	Sosman et al. (1969)
Sapele wood	–	1	Alvarez-Cuesta et al. (2004)
Family Moraceae			
Antiaris (*Antiaris africana or Antiaris toxicana*)	–	1	Higuero et al. (2001)
Iroko (*Cholophora excelsa*)	(*)	5	Ricciardi et al. (2003), Azofra and Olaguibel (1989), Pickering et al. (1972)
Family Oleaceae			
Ash (*Fraxinus americana*)	–	1	Malo and Cartier (1989), Fernández-Rivas et al. (1997), Spiewak et al. (1994)
Family Rhamnaceae			
Cascara sagrada bark (*Rhamnus purshiana*)	–	1	Giavina-Bianchi et al. (1997)
Family Rosacea			
Soapbark (*Quillaja saponaria*)	–	1	Raghuprasad et al. (1980)
Family Rutaceae			
Pau marfin (*Balfourodendron riedelianum*)	–	1	Basomba et al. (1991)
Family Sabotaceae			
Abiurana	–	2	Booth et al. (1976)
Makore, African cherry wood (*Tieghemella heckeli*)	–	–	Obata et al. (2000)
Tanganyika aningré	–	2	Paggiaro et al. (1981)
Family Sterculiaceae			
African Maple (*Triplochiton scleroxylon*), *W*hitewood, Samba, Obeche, Wawa	(*)	16	Quirce et al. (2000), Ferrer et al. (2001, Abstract), Pontier et al. (2002, Abstract), Hinojosa et al. (1986), Hinojosa et al. (1984), Reijula et al. (1994), Weber and Häußinger (1988)
Family Thymelaeceae			
Ramin (*Gonystylus bancanus*)	–	2	Hinojosa et al. (1986), Howie et al. (1976), Fasani et al. (1982, Abstract)
Softwood			
Family Cupressaceae			
California Redwood (*Sequoia semperivirens*)	–	–	Chan-Yeung and Abboud (1976), doPico (1978)
Eastern white cedar (*Thuja occidentalis*)	*	1	Malo et al. (1994), Cartier et al. (1986)
Western red cedar (*Thuja plicata*)	**	323	Ishizaki et al. (1973), Chan-Yeung et al. (1984), Noertjojo et al. (1996), Paggiaro and Chan Yeung (1987), Chan-Yeung et al. (1987), Chan-Yeung et al. (1982), Mue et al. (1975), Tse et al. (1982), Côté et al. (1990), Chan-Yeung et al. (1973), Gandevia and Milne (1970), Chan-Yeung and Desjardins (1992), Chan-Yeung et al. (1971), Pickering et al. (1972)

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Family Pinaceae			
Cedar of Lebanon (*Cedra libani*)	–	1	Greenberg (1972), Sosman et al. (1969)
Pine (*Pinus radiata*)	[*]	1	Douwes et al. (2001), Hessel et al. (1995), Spiewak et al. (1994), Skovsted et al. (2000), Schlünssen et al. (2004), Malo et al. (1986)
Mushrooms, Moulds (*fungi*)			
Edible mushrooms			
Boletus edulis	(*)	8	Symington et al. (1981), Foti et al. (2008), Torricelli et al. (1997)
Pleurotus cornucopiae	–	1	Michils et al. (1991)
Pleurotus ostreatus	–	1	Vereda et al. (2008)
Yeast			
Saccharomyces cerevisiae, powdered dehydrated yeast	–	1	Belchi-Hernandez et al. (1996)
Moulds, other fungi			
Aspergillus, various species	–	1	Klaustermeyer et al. (1977)
Aspergillus niger	*[*]	12	Topping et al. (1985), Seaton and Wales (1994)
Aspergillus fumigatus	–	1	Allmers et al. (1997), Baz et al. (1999)
Alternaria	[*]	8	Klaustermeyer et al. (1977), Menzies et al. (1997)
Chrysonilia sitophila, common red bread mould	–	3	Tarlo et al. (1996), Monzn et al. (2009), Francuz et al. (2010)
Dictyostelium discoideum, slime mould	–	1	Gottlieb et al. (1993)
Mucor	–	1	Enríquez et al. (2011)
Neurospora sp.	–	2	Côté et al. (1991), Heffler et al. (2009)
Penicillium camemberti	–	1	Merget et al. (2008)
Plasmopara viticola, pseudo mildew of grapevine	–	1	Wenzel Schaubschläger et al. (1994)
Rhizopus nigricans	–	1	Gamboa et al. (1996)
Scopulariopsis brevicaulis	–	–	Lander et al. (1988)
Sporobolomyces salmonicolor	–	–	Seuri et al. (2000, abstract)
Mould fungi (*Aspergillus and Mucor*)	–	–	Bergmann et al. (1976)
Microscopic organisms (Protoctistae)			
Chlorella (algae)	–	1	Ng et al. (1994)
Enzymes			
α-amylase from *Aspergillus oryzae*	**	29	Brisman et al. (2004), Nieuwenhuijsen et al. (1999), Houba et al. (1996), Losada et al. (1992), Baur et al. (1994), Brisman and Belin (1991), Moneo et al. (1995), Quirce et al. (2002), Valdivieso et al. (1994), Blanco Carmona et al. (1991), Birnbaum et al. (1988)
α-amylase inhibitors of cereal origin	–	3	López-Rico et al. (1998)
Amylase from *Bacillus licheniformis*	–	4	Hole et al. (2000)
Aspergillus enzymes (α-amylase, cellulase)	(*)	9	Quirce et al. (1992)
Aspergillus oryzae enzymes (amylase, protease)	–	1	Baur (1981)
β-glucanase and phytase	–	1	O'Connor et al. (2001)

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Bromelain of *Ananas comosus*	[*]	13	Gailhofer et al. (1988), Gailhofer et al. (1987), Galleguillos and Rodriguez (1978), Baur and Fruhmann (1979)
Cellulase, not specified	–	2	Tarvainen et al. (1991)
Cellulase from *Aspergillus niger*	–	2	Losada et al. (1986)
Cellulase from *Trichoderma reesei*	(*)	7	Vanhanen et al. (2000)
Cellulase from *Trichoderma viride*	[*]	2	Ransom and Schuster (1981)
Cellulase from *Trichoderma viridae* and *Fusarium moniliform*	–	1	Kim et al. (1999)
Detergent enzymes	*[*]	53	Brant et al. (2004), Adisesh et al. (2011, Abstract), Brant et al. (2009), Brant et al. (2006), Cullinan et al. (2000)
Enzyme powder in cheese production, fungal and pancreatic-based	–	2	Casper et al. (2008, Abstract)
Enzymes α-amylase and lysozyme	–	1	Santaolalla et al. (2002)
Enzymes (Amylase, Cellulase, Protease)	[*]	54	Cullinan et al. (2000)
Enzymes (α-amylase (bacterial), α-amylase (fungal), cellulase, phytase, xylanase)	[*]	1	Vanhanen et al. (1997)
Enzymes (amylase, bromelain, chymotrypsin, lipase, papain, trypsin)	–	4	Zentner et al. (1997)
Flaviastase from *Aspergillus niger*	–	3	Pauwels et al. (1978)
Glucoamylase (amyloglucosidase) from *Aspergillus niger*	–	4	Quirce et al. (2002a)
Glucose oxidase from *Aspergillus niger*	–	1	Baur (1981)
Lactase from Aspergillus	[*]	9	Muir et al. (1997)
Lysozyme (lysozyme chloride)	–	1	Park and Nahm (1997)
Pancreatin (porcine and bovine)	(*)	19	Park et al. (2002), Wiessmann and Baur (1985), Baur et al. (1984), Aiken et al. (1997)
Papain (*Carica papaya*)	**	109	Baur et al. (1982), Vogelmeier et al. (1985), Keenan et al. (1979), Novey et al. (1980), Baur and Fruhmann (1979), Milne and Brand (1975), Tarlo et al. (1978), Marchioli et al. (1977), Merget et al. (1995), Quinones et al. (1999, Abstract), Soto-Mera et al. (2000)
Pectinase from *Aspergillus niger*	–	2	Hartmann et al. (1983)
Pectinase from *Aspergillus niger* and glucanase from *Trichoderma*	–	3	Sen et al. (1998)
Pepsin (porcine)	–	3	Drexler and Beyer (1997), Anibarro Bausela and Fontela (1996), Cartier et al. (1984b)
Peptidase from *Serratia ssp.*	–	1	Park and Nahm (1997)
Phytase from *Aspergillus niger*	*[*]	12	Doekes et al. (1999), Baur et al. (2002)
Proteolytic enzymes derived from *Bacillus* species	–	–	Cathcart et al. (1997)

Table 3 continued

Taxonomical classification of agents	Strength of evidence per agent (three-star system of RCGP[a])	Total no. of allergic asthma cases per agent, *n*—specific sensitization is not confirmed	References[b]
Various enzymes from Bacillus subtilis (Alcalase, protease, maxatase, maxapem, esperase, cellulase, α-amylase, lipase, subtilisin)	**	327	Flood et al. (1985), Juniper et al. (1977), Newhouse et al. (1970), Slavin and Lewis (1971), Mitchell and Gandevia (1971), Greenberg et al. (1970), Zachariae et al. (1981), Pepys et al. (1973), Vanhanen et al. (2000), Liss et al. (1984), Dijkman et al. (1973), Pepys et al. (1969), Franz et al. (1971)
Proteolytic enzymes: Alcalase	(*)	6	Paggiaro et al. (1984, Abstract)
Protease, Pronase E from *Streptomyces griseus*	–	1	Kempf et al. (1999)
Rennet not specified and of *Endothica parasitica*	–	1	Niinimäki and Saari (1978), Jensen et al. (2006)
Trypsin (porcine), inactivated	*	4	Colten et al. (1975)
Xylanase from *Aspergillus niger*	–	3	Tarvainen et al. (1991), Baur et al. (1998)
Various enzymes	–	–	Baur et al. (1988)
Chemicals			
Drugs			
Aescin	–	1	Munoz et al. (2006)
α-methyldopa	–	1	Harries et al. (1979)
Aminophylline	–	1	Rosenberg et al. (1984)
Amprolium hydrochloride	–	1	Greene and Freedman (1976)
Cephalosporin	[*]	8	Briatico-Vangosa et al. (1981), Park et al. (2004), Coutts et al. (1981), Sastre et al. (1999), Stenton et al. (1995), Fracchia et al. (1996, abstract)
Cimetidine	–	–	Coutts et al. (1984)
Ciprofloxacin	–	1	Broding et al. (1996)
Hydralazine	–	–	Perrin et al. (1990)
Isonicotinic acid hydrazide (INH)	–	1	Asai et al. (1987)
Lasamide (Intermediate of Furosemide)	–	–	Klusácková et al. (2007)
Mitoxantrone	–	–	Walusiak et al. (2002)
Opiates	*[*]	28	Agius (1990), Biagini et al. (1992), Moneo et al. (1993), Romaguera and Grimalt (1983), Condé-Salazar et al. (1991), Ulinski et al. (1996), Agius (1989)
Penicillines	[*]	4	Shmunes et al. (1976), Møller et al. (1986), Stejskal et al. (1987 Davies et al. (1974), Jiménez et al. (1998), Vandenplas et al. (1997), Wüthrich and Hartmann (1982), Lagier et al. (1989), Moscato et al. (1995)
Phenylglycine acid chloride (side chain of Ampicillin, Cephalexin, cephaloglycin)	[*]	4	Kammermeyer and Mathews (1973)
Salbutamol base	–	–	Agius et al. (1994)
Salbutamol intermediate—glycyl compound powder: 2-(*N*-Benzyl-*N*-tert-butylamino)-4′-hydroxy-3′-hydroxymethylacetophenone diacetate			Fawcett et al. (1976)
Spiramycin	–	2	Malo and Cartier (1988), Moscato et al. (1984), Paggiaro et al. (1979), Davies and Pepys (1975)
Tetracycline	–	1	Menon and Das (1977)

Table 3 continued

Taxonomical classification of agents	Strength of evidence per agent (three-star system of RCGP[a])	Total no. of allergic asthma cases per agent, *n*—specific sensitization is not confirmed	References[b]
Thiamine	–	2	Drought et al. (2005)
Tylosin tartrate	–	1	Lee et al. (1989)
Polymyxin E (Colistin)	–	–	Gómez-Ollés et al. (2010)
Metals			
Aluminium	–	1	Simonsson et al. (1985, Abctract), Vandenplas et al. (1998)
Chromium	–	5	Park et al. (1994), Leroyer et al. (1998)
Chromium and nickel	(*)	13	Novey et al. (1983), Bright et al. (1997), Jesus Cruz et al. (2006), Fernandez-Nieto et al. (2006)
Chromate	–	–	De Raeve et al. (1998)
Cobalt	–	2	Gheysens et al. (1985), Wittczak et al. (2003), Krakowiak et al. (2005)
Cobalt and nickel	–	–	Shirakawa et al. (1990)
Iron	–	–	Muñoz et al. (2009)
Manganese	–	–	Wittczak et al. (2008)
Nickel sulphate	–	2	Malo et al. (1982), Block et al. (1982)
Platinum salts	**	96	Hunter et al. (1945), Pepys et al. (1972), Merget et al. (1988), Venables et al. (1989), Merget et al. (1991), Bolm-Audorffl et al. (1992), Niezborala et al. (1996), Cristaudo et al. (2005)
Palladium	–	1	Daenen et al. (1999)
Vanadium	–	–	Musk and Tees (1982, abstract)
Zinc	–	1	Malo and Cartier (1987), Malo et al. (1993, abstract)
Rhodium salts	–	1	Merget et al. (2010)
Dyes			
Carmine	**	11	Ferrer et al. (2005), Tabar-Purroy et al. (2003), Quirce et al. (1994), Acero et al. (1998), Stücker et al. (1996), Rodriguez et al. (1990), Burge et al. (1979), Añíbarro et al. (2003, abstract)
FD&C Blue Dye No. 2 (Indigotine)	–	1	Miller et al. (1996, abstract)
Henna (black)	–	1	Starr et al. (1997)
Lanasol dyes	–	4	Topping et al. (1989)
Monascus ruber	–	1	Vandenplas et al. (2000)
Reactive dyes	**	28	Alanko et al. (1978), Park et al. (1989), Romano et al. (1992), Nilsson et al. (1993), Park et al. (2007)
Biocides			
Chloramine T	(*)	9	Kujala et al. (1995), Blasco et al. (1992, abstract), Bourne et al. (1979)
Glutaraldehyde	–	1	Ong et al. (2004), Quirce et al. (1999), Gannon et al. (1995), Chan-Yeung et al. (1993)
Chlorhexidine	–	–	Waclawski et al. (1989)
Hexachlorophene	–	1	Nagy et al. (1984)
Ortho-phthalaldehyde	–	–	Fujita et al. (2006)
Peracetic acid, hydrogen peroxide	–	–	Cristofari-Marquand et al. (2007)

Table 3 continued

Taxonomical classification of agents	Strength of evidence per agent (three-star system of RCGP[a])	Total no. of allergic asthma cases per agent, *n*—specific sensitization is not confirmed	References[b]
Fungicides			
Tetrachloroisophthalonitrile	–	–	Honda et al. (1992)
Captafol	–	–	Royce et al. (1993)
Tributyl tin oxide (TBTO)	–	–	Shelton et al. (1992)
Fluazinam and chlorothalonil	–	–	Draper et al. (2003)
Isocyanates			
Toluene diisocyanates (TDI)	**	9	Zedda et al. (1976), Siracusa et al. (1978), Baur et al. (1981), Moscata et al. (1991)
Hexamethylene diisocyanate (HDI)	*	3	Vandenplas et al. (1993)
1,5-naphthalene diisocyanate (NDI)	–	–	Harries et al. (1979), Baur et al. (2000, 2001)
Methylene diphenyldiisocyanate (MDI)	*[*]	10	Stingeni et al. (2008), Donnelly et al. (2004), Perfetti et al. (2003), Valks et al. (2003), Liss et al. (1988), Tse et al. (1985), Zammit-Tabona et al. (1983, abstract)
Triglycidyl isocyanurate (TGIC)	–	–	Piirila et al. (1997)
Various isocyanates	*[*]	22	Cartier et al. (1989), O'Brien et al. (1979), Pezzini et al. (1984), Deschamps et al. (1998), Tee et al. (1998), Minov et al. (2008)
Anhydrides			
Tetrachlorophthalic anhydride	(*)	7	Schlueter et al. (1978), Howe et al. (1983)
Phthalic anhydride	*[*]	6	Maccia et al. (1976, abstract), Ward and Davies (1982), Wernfors et al. (1986), Nielsen et al. (1988)
Phthalic anhydride and chlorendic anhydride	–	1	Keskinen et al. (2000)
Methyl tetrahydrophthalic anhydride (MTHPA)	*	3	Nielsen et al. (1989), Nielsen et al. (1992)
Hexahydrophthalic anhydride	*	5	Moller et al. (1985), Chee et al. (1991)
Maleic anhydride	–	1	Lee et al. (1991)
Trimellitic anhydride	[*]	4	Zeiss et al. (1977)
Various anhydrides	–	–	Fawcett et al. (1977)
Amines			
Amino-ethyl ethanolamine	–	–	Pepys and Pickerting (1972)
Dimethyl ethanolamine	–	–	Vallieres et al. (1977, abstract)
Ethylenediamine	–	2	Lam and Chan-Yeung (1980, abstract), Nakazawa et al. (1991, abstract)
Ethanolamine and Triethanolamine	–	–	Savonius et al. (1994)
Diethanolamine	–	–	Piipari et al. (1998)
Paraphenylenediamine	–	–	Silbermann and Sorrell (1959)
Piperazine	–	–	Hagmar et al. (1982)
Piperazine dihydrochloride	–	1	Pepys et al. (1972)
Piperazine and *n*-methyl-piperazine	–	2	Welinder et al. (1986)
Piperazine citrate	–	1	Quirce et al. (2006)
Other chemicals compounds			
Azodicarbonamide	–	–	Slovak (1981), Malo et al. (1985), Normand et al. (1989), Kim et al. (2004)
Epoxy resin	–	1	Hannu et al. (2008)

Table 3 continued

Taxonomical classification of agents	Strength of evidence per agent (three-star system of RCGP[a])	Total no. of allergic asthma cases per agent, *n*—specific sensitization is not confirmed	References[b]
Formalin, formaldehyde	–	1	Hendrick et al. (1975), Hendrick et al. (1975), Burge et al. (1985), Nordman et al. (1985), Grammer et al. (1993), Kim et al. (2001)
Persulphate salts and henna	–	2	Pepys et al. (1976)
Persulphate salts	*	19	Parra et al. (1992), Schwaiblmair et al. (1997), Munoz et al. (2003), Moscato et al. (2005)
Polyfunctional aziridine	*	4	Kanerva et al. (1995)
Worksites			
Farming			
Farming: animals, cereal, hay and straw, storage mites	**	30	Walusiak et al. (2004
Co-exposure to various laboratory animals	***	140	Gautrin et al. (2001), Gautrin et al. (2002), Botham et al. (1987), Kruize et al. (1997), Renström et al. (1994), Renström et al. (1995), Aoyama et al. (1992), Venables et al. (1988), Agrup et al. (1986), Fuortes et al. (1996), Beeson et al. (1983), Lutsky et al. (1975), Davies and McArdle (1981), Gross (1980), Lincoln et al. (1974), Slovak and Hill (1981), Sjösted and Willers (1989), Krakowiak et al. (2002), Krakowiak et al. (1997, abstract)
Bakery			
Alkaline hydrolysis wheat gluten derivative	–	–	Lachance et al. (1988)
Bakery (flour, amylase, storage mites)	**	174	Brisman et al. (2000), Brisman et Järvholm (1995), Cullinan et al. (2001), Brisman et al. (2003), Houba et al. (1998), Cullinan et al. (1994), Talini et al. (2002), Musk et al. (1989), Smith et al. (1997), Droste et al. (2003), De Zotti et al. (1994), Jeffrey et al. (1999), Prichard et al. (1984), Storaas et al. (2005), Houba et al. (1996: Prichard et al. (1985), Baur et al. (1998), Brant et al. (2005), Järvinen et al. (1979), Bohadana et al. (1994), Hur et al. (2008)
Barley (*Hordeum vulgare*)	–	–	Vidal and González-Quintela (1995)
Buckwheat (*Fagopyrum esculentum* or *schulentum*)	–	4	Schumacher et al. (1993), Valdivieso et al. (1989), Park and Nahm (1996), Choudat et al. (1997, abstract)
Rye flour (*Secale cereale*)	(*)	7	Armentia et al. (1997), Letran et al. (2008)
Soybean processing (Bakery, animal feeding, food processing)			
Soybean (hulls, flour, enzymes)	*[*]	25	Zuskin et al. (1988), Zuskin et al. (1991), Maggio et al. (2003), Codina et al. (2000), Baur et al. (1996), Lavaud et al. (1994), Quirce et al. (2002), Quirce et al. (2000), Roodt and Rees (1995), Bush et al. (1988), Bush et al. (1977)
Brewery			
Brewery	–	–	Godnic-Cvar et al. (1999)
Welding			
Stainless steel welding fumes	–	–	Hannu et al. (2007)

Table 3 continued

Taxonomical classification of agents	Strength of evidence per agent (three-star system of RCGP[a])	Total no. of allergic asthma cases per agent, *n*—specific sensitization is not confirmed	References[b]
Others			
Soft corrosive soldering fluxes: zinc chloride and ammonium chloride	–	–	Weir et al. (1989)

(*) upgrading from "−" due to at least 5 reported asthma cases without contradictory finding

[a] [] downgrading due to lower quality of clinical investigations

[b] Detailed references in online supplement

Table 4 Overview of the number of agents, worksites or professions graded by the modified RCGP three-star system

Evidence level (modified RCGP three-star grading)	Number of agents, worksites or professions belonging to the respective RCGP grade	
***	1	Co-exposure to various lab animals
**	18	α-amylase from Aspergillus oryzae, various enzymes from *Bacillus subtilis*, papain, bakery (flour, amylase, storage mites), western red cedar, latex, psyllium, farming (animals, cereal, hay, straw and storage mites), storage mites, rat, carmine, egg proteins, atlantic salmon, fishmeal, norway lobster, prawn, snow crab, seafood, trout and turbot, reactive dyes, toluene diisocyanates (TDI), platinum salts.
*[*]	17	Detergent enzymes, soybean (hulls, flour), paprika, tea dust, tobacco, *Aspergillus niger*, cow, predatory mites, spider mites, opiates, methylene diphenyl diisocyanate (MDI), phthalic anhydrides, various isocyanates
*	18	Eastern white cedar, various flowers, guar gum, poppy, rose (*Rosa rugosa*), senna, ispaghula husks, sunflower pollen, trypsin, various wood (abies, chestnut, douglas, framire, mansonia, oak, obeche, walnut, white poplar), weeping fig, non-biting midges, hexahydrophthalic anhydride, hexamethylene diisocyanate (HDI), methyl tetrahydrophthalic anhydride (MTHPA), persulphate salts, polyfunctional aziridine
[*]	24	Alternaria, bromelain of *Ananas comosus*, cellulase from *Trichoderma viride*, lactase from aspergillus, various enzymes, chrysanthemum, castor beans, madagascar jasmine, pine, flowers, budgerigar, flour moth, house dust mites, mouse, poultry, red soft corals, screw-worm fly, shrimp, various birds, cephalosporin, penicillines, phenylglycine, acid chloride, trimellitic anhydride
(*)	19	Aspergillus enzymes, cellulase from *Trichoderma reesei*, pancreatin, proteolytic enzymes, asparagus, boletus edulis, carnation, garlic dust, rye flour, gum arabic, iroko, various woods, african maple, black bat, mealworm, poultry mites, tetrachlorophtalic anhydride, chloramine T, chromium and nickel
–	275	

agents (Allmers et al. 2002; LaMontagne et al. 2006; Tarlo 2007; Quint et al. 2008; Baur et al. 2012b).

To our knowledge, this is the first evidence-based approach to connect occupational asthma with its causes.

The 865 publications retrieved from our Medline/PubMed and additional database search refer to 682 partially overlapping individual agents, 121 "mixed" agents and 62 worksites resulting in 372 different causes of allergic occupational asthma. Following our evaluation criteria, diagnoses of occupational allergic asthma could be confirmed in 664 studies.

Strength and limitations

We identified a large field of occupational agents causing allergic asthma and evaluated the strength of the body of

evidence for each agent listed using the RCGP three-star system. This approach is the main strength of this work. Seeing that the concept of evidence-based medicine is omnipresent in contemporary clinical research and practice, we applied this evaluation for grading causes of occupational asthma. We only considered cases to be caused by the investigated agent if there was evidence for both asthma and sensitisation. There are some limitations to such an approach, in particular the underevaluation of certain types of medical reports and the generalisability of the results obtained in this manner. Furthermore, bias in the selection of information, publication content (e.g. exposure to multiple agents) and sample population (healthy hired and healthy worker effects) cannot be excluded. Since the quality and the content of considered studies vary widely, it can sometimes be difficult to combine them and generalise the results. Unfortunately, the source of the agent is not always clearly indicated in publications. In certain confinements (e.g. in swine confinement) or professions, causative agents are not always clear and may comprise different allergens as well as irritants. The same is true for exposure to mixtures of components as is the case in many workplaces (e.g. in the production of plastics or polyurethanes where there may be isocyanates, polyalcohols or solvents as well as irritative gases in the atmosphere).

The evidence levels for causing allergic occupational asthma of many of the listed agents or worksites are moderate to low. Approximately one quarter of the identified studies represent scientific studies. This is due to the fact that randomised controlled trials as claimed in scientific discussion (Tarlo et al. 2008) would have been unethical for studying exposure effects of harmful agents. Therefore, high-quality studies are missing and the available studies sometimes included only a few numbers of cases. The majority of them were surveys, case series or case reports with evidence level rated very low. The common diagnostic procedure for occupational asthma in clinical settings is a stepwise approach including questionnaires with asthma-specific symptoms as well as respiratory and allergological assessment. Objective diagnostic findings such as SPT, specific IgE, lung function parameters and SIC were not frequently applied resulting in limitations in classifying occupational asthma as being due to IgE-mediated sensitisation. Self-reported work-related symptoms are relatively sensitive for a diagnosis of occupational asthma; however, the specificity is low (Tarlo et al. 2008). In 291 of the 865 studies (33.6 %) included in this work, self-reported asthma symptoms or physician-reported asthma were used as a diagnostic approach. Serial spirometric or peak flow measurements (sPFT) which also comprise high sensitivity and specificity (Baur et al. 2012b; Burge et al. 2012) were identified in 186 studies. The SIC or sPFT gold standards were only applied in half of the studies. We included low SIGN grade studies (3/3+) if high level of evidence was missing because they may provide useful information for managing new cases of asthma.

The level of evidence for single agents depends on the number of publication included. Agents for which the research activity is higher obtain higher levels in our rating (Quint et al. 2008). An absence or a low evidence grade of an occupational agent (e.g. in studies without SIC or proven IgE-mediated sensitisation) does not necessarily exclude its potential for causing IgE-mediated asthma. This also comprises the need for modification of grading systems for evidence-based grading of the literature if high-level studies cannot be expected; a Delphi conference including experts world-wide could be an alternative approach.

Comparison with previous reviews and overviews of allergenic occupational asthma agents

A continuously updated classification of allergenic occupational asthma agents has been provided by the American Conference of Industrial Hygienists (ACGIH), the European Community and the Health and Safety Executive (ACGIH® http://www.acgih.org; Europäische Gemeinschaft 2001; Deutsche Forschungsgemeinschaft (DFG) 2011; Health and Safety Executive (HSE) 2001; Baur 2008). Allergenic agents are listed in three categories: substances which were considered to meet the EU criteria and labelled with H334 (till 2011 R42), substances which did not meet these criteria and those which were on account of concerns over respiratory sensitisation. Several groups have already published lists of airway sensitising agents (van Kampen et al. 2000; Tarlo and Malo 2009; Quirce and Sastre 2011; Baur 2008; Bernstein et al. 2006; Malo and Chan-Yeung 2009).

Quirce and Sastre recently summarised the new causative agents published between 2009 and 2011. These reviews all lacked an evidence-based evaluation of the clinical literature of identified agents. Therefore, even if the previous reviews already cover approximately 300 allergenic occupational asthma agents, the approach of the present work is more comprehensive, by listing 372 agents and with the advantage of grading each identified agent, worksite or profession in a well-defined evidence-based manner related to causation of occupational asthma.

Concluding remarks

Occupational asthma has a great impact on the socio-economic status of the workers concerned, the healthcare system and the society. In 2008, the costs in Germany for

occupational disease "Obstructive respiratory tract diseases caused by allergenic substances", listed as occupational disease no. 4301, were €52.1 million (Deutsche Gesetzliche Unfallversicherung (DGUV) 2009). This includes compensation for confirmed cases, costs of rehabilitation and preventive interventions. In 2003, Great Britain experienced a total of 631 new occupational asthma cases resulting in costs of about £3.4 to £4.8 million per year over the lifetime of the diseased patient (Boyd et al. 2006).

In 2010, 2,045 claims referring to the occupational disease no. 4301 were officially reported to German accident insurance institutions. Three hundred and twelve cases were acknowledged as new cases of the occupational disease no. 4301, representing only about 15 % of total cases. There were also 119 claims referring to occupational disease no. 1315 (isocyanate-induced diseases) with 30 acknowledged cases, representing about 25 % of total cases. It can be assumed that the official number of allergic occupational asthma cases is significantly higher since in routine diagnostics, objective tests are frequently not available and not applied or a referral to specialised diagnostic centres is not initiated. Primary care physicians are often unaware of the presence of causative agents in the workplace and do not frequently enquire into occupational history using valid questionnaires and a comprehensive diagnostic setup.

To facilitate the identification of occupational asthma agents and to improve preventive measures as well as management in affected cases, causative conditions must be easily available (Heederik et al. 2012). This study summarises the current levels of evidence for individual agents and worksites causing allergic occupational asthma. We found moderate to strong evidence for laboratory animals, several enzymes, isocyanates, farming and bakeries among others. It may help physicians in identifying a suspected allergenic agent as causative and may in such cases initiate a more detailed examination. It also demonstrates that more work is needed to fill in specific gaps, for example, in studying all potential asthma-inducing agents, and that objective diagnostic methods are available but need to be better integrated into clinical practice. Our comprehensive list could be the basis for surveillance programmes of exposed workers in order to identify those at higher risk of developing occupational asthma and to apply appropriate secondary preventive measures (Baur et al. 2012b).

It is hoped that this work provides a relevant contribution to prevention resulting in significant reduction or even elimination of occupational asthma development due to causative exposures, which is the most straightforward approach to reducing the burden of this disease.

Conflict of interest The authors declare that they have no conflict of interest.

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