A reference document of the relation between potential sensitizing occupational exposures and asthma

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FOREWORD

The National Board of Industrial Injuries and the Occupational Diseases Committee in Denmark have requested a detailed scientific reference document of the causality between potential occupational sensitizing exposures and asthma. According to the National Board of Industrial Injuries and the Occupational Diseases Committee, specific guidelines are currently needed as to which occupational sensitizing exposures are associated with an increased risk of asthma, and when exposures are sufficient to cause asthma. Specific guidelines for clinical evaluation of patients with asthma suspected to be caused by occupational sensitizing exposures are also needed.

The reference document was conducted by PhD, post.doc. Annett Dalbøge, Professor Henrik Kolstad, and Professor Vivi Schlünssen together with a scientific forum comprising experts in asthma. The scientific forum included MD David Sherson, Department of Occupational and Environmental Medicine and Department of Pulmonary Medicine, Odense University Hospital, Professor Torben Sigsgaard, Department of Public Health, Environment, Occupation and Health, Danish Ramazzini Centre, Aarhus University, Professor Charlotte Suppli Ulrik, Department of Pulmonary Medicine, Hvidovre Hospital, MD PhD Harald William Meyer, Department of Occupational and Environmental Medicine, Bispebjerg Hospital, Copenhagen, MD dr.med. Niels Ebbehøj, Department of Occupational and Environmental Medicine, Bispebjerg Hospital, Copenhagen. Senior consultant, MD, PhD Hille Suojalehto, Finnish Institute of Occupational Health, Helsinki, Finland and senior researcher PhD Jan-Paul Zock, ISGlobal Institute for Global Health, Barcelona, Spain as well as IRAS (Institute for Risk Assessment Science), Utrecht University, the Netherlands independently evaluated the reference document. We followed specific guidelines for preparation of the document and quality approval provided by the Danish Work Environment Fund. The Danish Work Environment Fund granted the conduction of the reference document.

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1. BACKGROUND

1.1 Asthma

Asthma is a chronic inflammatory disorder of the airways, which is associated with airway hyper-responsiveness and variable airflow obstruction that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing.[1, 2] Asthma is common among both children and adults, and it is estimated that around 300 million people worldwide suffer from asthma.[3] Point prevalence of parent-reported physician-diagnosed asthma among 7-year-old children in Denmark is about 12 %,[4] while the incidence of asthma defined by admissions or use of asthma medication among 5-14 year old children residing in Denmark is 18/1000 person-years (PY).[5] For adults, global prevalence of asthma range between 1 % and 21 %.[6] The point prevalence of self-reported current asthma among adults in the Nordic countries is 5-10 % (6 % in Denmark), and steadily increasing from 1990-2010 with no clear difference for different birth cohorts.[7] The incidence of self-reported asthma among adults in the Nordic countries is 2/1000 PY.[8] Occupational groups with high incidence proportion of asthma includes nurses (4.8 %), wood workers (3.9 %), printers (3.6 %), cleaners and care takers (3.4 %), and agricultural and forestry workers (3.1 %).[9]

Approximately 10-15 % of adult asthma can be attributed to occupational exposures.[10-12] This asthma group is also known as work-related asthma. It includes occupational asthma defined as new onset of asthma due to exposures in the workplace, and work-aggravated asthma defined as worsening of pre-existing or concomitant non-occupational asthma by exposures in the workplace. Two types of work-related asthma are distinguished based on their appearance with or without a latency period. Asthma appearing after a latency period is in most cases caused by most high-molecular-weight (HMW) and by certain low-molecular-weight (LMW) exposures for which an allergic [immunoglobin E (IgE)-mediated] mechanism has been proven, but can also be induced by other less well known specific immunological mechanisms. Asthma without a latency period includes irritant-induced asthma, which may occur after single or multiple exposures to nonspecific irritants at high concentrations.[13]

1.2 Risk factors

The relation between occupational sensitizing exposures and asthma has been studied in numerous studies and include a large number of exposures. Several hundred occupational sensitizing exposures have been suspected to cause asthma including HMW sensitizing exposures from animals, fish, plants, enzymes, and mites, and LMW sensitizing exposures from wood, chemicals, and metals.[14, 15] In a comprehensive review of 372 potential occupational sensitizing exposures, Baur *et. al.* (2014)[15] found strong evidence of a relation for exposure to various laboratory animals, moderate evidence for 35 exposures, limited or very limited/contradictive evidence for 61 exposures, and no evidence for the remaining exposures. New occupational sensitizing exposures are continually being reported; therefore, a systematic update of the current list of occupational sensitizing exposures together with the level of evidence for each exposure may assist companies, Occupational Health and Safety Institutions, and regulating bodies in preventing asthma. An updated list might also help physicians in diagnosing and managing workers suffering from occupational asthma.

Other risk factors might also cause asthma. Genetic disposition is regarded the strongest risk factor,[16] but environmental risk factors as common inhalant sensitizing exposures, tobacco smoke, air pollution are also well documented risk factors for development of asthma.[17]

1.3 Clinical evaluation

The clinical evaluation of asthma typically includes a combination of patient history, lung function tests, evaluation of sensitization, and might be combined with biomarkers from exhaled breath, bronchial lavage, or blood samples.[18] In persons where asthma is suspected to be caused by occupational sensitizing exposures, the key issue is to investigate the relation between the occupational sensitizing exposure under suspicion and the asthma disease. This includes the patient history, repeated lung function tests (e.g., forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF)) at home and at work, an allergological evaluation with skin prick test, specific IgE measurement, histamine release test, and/or basophil activation test. Sometimes a specific inhalation challenge test with the suspected occupational sensitizing exposure is needed.[19, 20]

2. AIM AND HYPOTHESIS

The aim of this reference document was to investigate the relation between potential occupational sensitizing exposures and the development of asthma (study I and II), and to generate guidelines for clinical evaluation of patients with asthma suspected to be caused by occupational sensitizing exposures (study III). Three studies were undertaken with the following specific aims:

Study I: To conduct an overview of systematic reviews to summarize the existing evidence of the relation between potential occupational sensitizing exposures and the development of asthma in the working population.

Study II: To conduct a systematic review of the relation between asthma and 10 potential occupational sensitizing exposures classified as having no or limited evidence in the overview of systematic reviews.

Study III: To generate guidelines for clinical evaluation of patients with asthma suspected to be caused by occupational sensitizing exposures.

The hypothesis was that we would find evidence for a relation between several occupational sensitizing exposures and asthma.

3. MATERIALS AND METHODS

An overview of materials and methods of the three studies (I-III) included in the reference document is given in table 2 with additional information available in the following sections and in the appended papers (I-III).

Table 1. Overview of materials and methods of each study in the reference document

	Study I	**Study II**	**Study III**
Aim	To summarize the existing evidence of the relation between potential occupational sensitizing exposures	To study the relation between asthma and 10 potential occupational sensitizing exposures classified as having no or limited evidence in the overview of systematic reviews (study I)	To generate guidelines for clinical evaluation of patients with asthma suspected to be caused by occupational sensitizing exposures
Design	Overview of systematic reviews	Systematic review	Narrative review
Searched databases	EMBASE, Medline/ PubMed, WoS, Cochrane	EMBASE, Medline/ PubMed, WoS	No systematic search conducted
Included no of studies	22	37	Not relevant
Population	Persons in or above working age	Persons in or above working age	Persons in or above working age
Outcome	Asthma	Asthma	Asthma
Outcome assessment	Self-reported or clinically assessed	Self-reported or clinically assessed	Clinically assessed
Exposure	Potential occupational sensitizing exposures	Ten potential occupational sensitizing exposures	Potential occupational sensitizing exposures
Exposure assessment	Subjective or objective	Subjective or objective	Subjective or objective

WoS; Web of science

Protocol and registration

The three studies followed the specific guidelines for preparation and quality approval provided by the Danish Work Environment Fund, supplemented by guidelines from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[21] The study protocol for all three studies was registered in PROSPERO (CRD42017057014).

3.1 Study I

Literature search, eligible criteria, and exclusion of studies

We constructed a PECO (Population, Exposure, Comparison, Outcome) which included a population in or above working age, potential occupational sensitizing exposures, a comparison between occupational sensitizing exposures and asthma, and self-reported or clinically assessed asthma (appendix 1, paper I). In collaboration with a librarian, we performed a systematic literature search for peer-reviewed systematic reviews published before the 29th of august 2017. The literature search was performed in the National Library of Medicine (MEDLINE/PubMed), Embase, Web of Science (WoS), and Cochrane (appendix 2, paper I). All potentially relevant articles were transferred to the online software tool Covidence (https://www.covidence.org). Duplicate articles were excluded, and identification of relevant articles was performed in three steeps; title screening, abstract screening, and full paper reading by two independent reviewers (appendix 3, paper I). We only included systematic reviews, defined as comprising a systematic literature search performed in one or more international electronic databases. We extended the literature search by screening the reference lists of all reviews included.

Data extraction and methodological quality assessment of each review

From each included review, we extracted core study information (e.g., searched databases, included number of studies, study designs, populations, exposures, and outcome), measure of association, and study conclusion. For approximately 25 % of the included reviews, data extraction was performed independently by two reviewers. For the remaining reviews, study data was extracted by one reviewer and quality check by another reviewer. The methodological quality of each included review was assessed independently by two reviewers using the quality assessment tool AMSTAR 2; a 16-item tool designed to appraise the methodological quality of systematic reviews.[22]

Quality of evidence of the relation between sensitizing exposures and asthma across reviews

We divided the exposures into main exposure groups according to the grouping performed by Baur et. al. (2014).[15] The quality of evidence of the relation between asthma and main groups (e.g., mammals) and subgroups/specific exposures (e.g., bats, cows, deer, elks) was assessed by two reviewers using a modification of the Royal College of General Practitioners' (RCGP) system of the British Occupational Health Research Foundation.[15, 23]

3.2. Study II

Literature search, eligible criteria, and exclusion of studies

We constructed a PECO (appendix 1, paper II) in which the population, comparison, and outcome were identical to the definition used in study I. Ten potential occupational sensitizing exposures classified as having no or limited evidence of a relation in the overview of systematic reviews (study I) were selected. We prioritized frequent potential occupational sensitizing exposures, suspected LMW exposures, and exposures which are not considered well known causes of asthma. The literature search was conducted in three databases i.e., the National Library of Medicine (MEDLINE/PubMed), Embase, and WoS (appendix 2, paper II) for studies published between the 1st of January 2011 and 7th of June 2019; July 2011 was the date of the literature search in Baurs review.[15] In Covidence, article duplicates and studies published before July 2011 were excluded. Two reviewers independently excluded studies based on title/abstract screening and full paper reading (appendix 3, paper II). We screened the reference lists of all included studies for additional relevant articles.

Data extraction and risk of bias assessment for each study

From each included study, two reviewers extracted study information (e.g., study design, population, outcome, exposure, confounders, and exposure-response relation). The methodological quality of each included study was independently assessed by two reviewers using a "risk of bias" tool developed for this study. This tool included 10 items; item 1-9 were scored "high" or "low", while item 10 was a subjective rating of the overall confidence in study results based on item 1-9 (appendix 4, paper II).

Quality of evidence of a relation across studies

For each study, we extracted information of the measure of association between potential occupational sensitizing exposures and asthma. Two reviewers upgraded or downgraded the level of evidence of the relation for main exposure groups (e.g., mammals) and subgroups/specific exposures (e.g., mouse) identified in our overview of systematic review using a modification of the RCGP.[14, 15]

3.3 Study III

The study was a narrative review conducted by the authors of this reference document, based on the expertise as clinicians and scientists within asthma and occupational medicine.

4. RESULTS

The following section summarises the main results of each of the three studies.

4.1 Study I

Literature search and exclusion of studies

The literature search included 2591 articles with 477 duplicates, providing 2114 potentially relevant articles. After title screening, 1537 articles were excluded, and 577 articles were moved to abstract screening. After abstract screening and full paper reading, we excluded additional 523 and 32 articles, respectively, providing a total of 22 systematic reviews to be included in our overview (figure 1, paper I).

Study characteristic and methodological quality of each included study

The 22 included systematic reviews covered 1198 studies and 486 sensitizing exposures (table 1, paper I). The overall confidence in review results was rated "high" for three, "moderate" for five, and "low" for 14 reviews.

Relation between sensitizing exposures and asthma across studies

We found strong evidence of a relation between main group of wood dust and asthma, and moderate evidence for mites and fish. For the subgroups/specific exposures, we found strong evidence for exposure to laboratory mites, and moderate evidence for 55 subgroups/specific exposures; *animals*; crustaceans (i.e., prawns and snow crabs), insects (i.e., locust and silkworm), mites (i.e., predatory mites, spider mites, and storage mites), fish (i.e., Atlantic salmon, seafood, fishmeal, trout, and turbot), mammals (i.e., cows and rats), animal products (i.e., egg proteins), *plants*; (i.e., latex, psyllium, coffee raw, paprika, tobacco, various tea dust, and western red cedar), "*mould, fungi and yeast"* (i.e., *Aspergillus, Cladosporium*, and *Penicllium genera*), *enzymes* (i.e., a-amylase from Aspergillus oryzae, detergent enzymes, papain, phytase from Aspergillus niger, and various enzymes from Bacillus subtilis), *drugs* (i.e., opiates), *metals* (i.e., platinum salts), *dyes* (i.e., carmine and reactive dyes), *isocyantes* (i.e., toluene diisocyanates, methylene diphenyl-diisocyante, and various isocyanates), anhydrides (i.e., phthalic anhydride), other chemical compounds (i.e., cleaning products: cleaning spray, bleach, mixing products, glutaraldehyde, formaldehylde, chlormine-T, and quanternary ammonium compounds), exposures in occupations/worksites (i.e., farming (animals, cereal, hay/straw, and storage mites), bakery (flour, amylase, and storage mites), and soybean (hulls, flour, and enzymes) (table 2).

Table 2: Overview of the level of evidence of the relation between main groups and subgroups/specific exposures based on the overview of systematic reviews

Evidence level	Main and subgroup/specific exposures
Strong evidence	*Main group:* Wood dust *Subgroup/specific:* Exposure to laboratory animals
Moderate evidence	*Main group:* Mites, Fish *Subgroup/specific:* Crustaceans: prawns, snow crabs, Insects: locust, silkworm, Mites: predatory mites, spider mites, storage mites, Fish: Atlantic salmon, seafood, fishmeal, trout, turbot, Mammals: cows, rats, Animal products: egg proteins, Plants: latex, psyllium, coffee raw, paprika, tobacco, various tea dust (various), western red cedar, "Mould, fungi and yeast": *Aspergillus, Cladosporium, Penicllium* genera, Enzymes: a-amylase from Aspergillus oryzae, detergent enzymes, papain, phytase from Aspergillus niger, various enzymes from Bacillus subtilis, Drugs: opiates, Metals: platinum salts, Dyes: carmine, reactive dyes, Isocyantes; toluene diisocyanates, methylene diphenyl-diisocyante, various isocyanates, Anhydrides: phthalic anhydride, Other chemical compounds: cleaning products: cleaning spray, bleach, mixing products, disinfectants including glutaraldehyde, formaldehylde, chloamine-T, quanternary ammonium compounds, Exposures in occupations/worksites; farming (animals, cereal, hay/straw, storage mites), bakery (flour, amylase, storage mites), and soybean (hulls, flour, enzymes)
Limited/contradictory evidence	*Main group:* Crustaceans, Other arachnida, Birds, Enzymes, Dyes, Isocyanates, Anhydrides, "Other chemicals compounds", Occupation/ worksites
No scientific evidence	*Main group:* Insects, Molluscs, Amphibians, Mammals, Animal products, Plants (not wood dust), "Mould, fungi, yeast", Drugs, Metals, Biocides, Amines

The level of evidence for subgroups/specific exposures are only presented for exposures with moderate to strong level of evidence.

4.2. Study II

Literature search and exclusion of studies

A total of 2904 articles were identified from the three databases. We excluded 220 duplicates and 128 articles published before July 2011. After title/abstract screening and full paper reading, we additional excluded 2421 and 98 articles, respectively, providing a total of 37 articles for our review (figure 1, paper II).

Study characteristic and risk of bias of each included study

The 37 included studies comprised seven cohort studies, three case-control studies, 10 cross-sectional studies, and 17 case-reports or case-series studies (table 1, paper II). Our overall confidence in study results was rated "high" in five, "moderate" in 13, and "low" in 19 studies. The most frequent items scored "high" were assessment of potential information bias, exposure specificity, and objective assessment of variability of lung function. The most frequent items scored "low" were assessment of risk factors for incident asthma, assessment of exposure-response relation, and adjustment of specific confounders.

Relation between sensitizing exposures and asthma across studies

Seven of 10 selected occupational sensitizing exposures were studied in the 37 included studies; no studies were found for amines, anhydrides, and molluscs. For the seven studied potential occupational sensitizing exposures, we upgraded main groups of crustaceans and enzymes to moderate evidence, and mammals, metal, and "mold, fungi and yeast" to limited/contradictory evidence. For specific subgroups/specific exposures, we upgraded pesticides, specific cleaning agents (i.e., chloramine and disinfection products), and an unspecified group of other chemicals (i.e., acrylates) to moderate evidence. For the remaining exposures, we did not change the level of evidence.

The updating the list of potential occupational sensitizing exposures now shows strong evidence of a relation with asthma for main groups of wood dust, and moderate evidence for main groups of mites, fish, crustaceans, and enzymes. For subgroups/specific exposures, we found strong evidence for exposure to various laboratory animals, while moderate evidence was found for 60 subgroups/specific exposures (table 3).

Table 3: Updated overview of the level of evidence for the relation between main groups and subgroups/specific exposures based on the overview and systematic review

Evidence level	Main and subgroup/specific exposures
Strong evidence	*Main group:* Wood dust *Subgroups/specific:* Exposure to laboratory animals
Moderate evidence	*Main group:* Mites, Fish, Crustaceans, Enzymes *Subgroups/specific:* Crustaceans: prawns, snow crabs, Insects: locust, silkworm, Mites: predatory mites, spider mites, storage mites, Fish: Atlantic salmon, seafood, fishmeal, trout, turbot, Mammals: cows, rats, Animal products: egg proteins, Planter: latex, psyllium, coffee raw, paprika, tobacco, various tea dust, western red cedar, Mould, fungi and yeast: Aspergillus, Cladosporium, Penicllium genera, Enzymes: a-amylase from Aspergillus oryzae, detergent enzymes, papain, phytase from Aspergillus niger, various enzymes from Bacillus subtilis, Drugs: opiates, Metals: platinum salts, Dyes: carmine, reactive dyes, Biocides: pesticides, Isocyantes: toluene diisocyanates, methylene diphenyl-diisocyante, various isocyanates, anhydrides: phthalic anhydride, Other chemical compounds: cleaning products: cleaning spray, bleach, mixing products, glutaraldehyde, formaldehylde, chloamine-T, quanternary ammonium compounds, chloramine, disinfection products), Exposures in occupations/worksites; farming (animals, cereal, hay/straw, storage mites), bakery (flour, amylase, storage mites), and soybean (hulls, flour, enzymes), Other chemicals: Unspecified group of other chemicals (acrylates)
Limited/contradictory evidence	*Main group:* Other arachnida, Birds, Dyes, Isocyanates, Anhydrides, "Other chemicals compounds", Occupation/worksites Mammals, Metals, "Mould, fungi, yeast" (without specification)
No scientific evidence	*Main group:* Insects, Molluscs, Amphibians, Animal products, Plants (not wood dust), Drugs, Biocides, Amines

The level of evidence for subgroups/specific exposures are only presented for exposures with moderate to strong level of evidence.

4.3 Study III

Clinical diagnose of occupational asthma

The clinical diagnosis of occupational asthma includes two parts: A) Verification of the asthma diagnosis, and B) Verification that asthma is caused by occupational exposures. However, in some cases the asthma diagnosis is first evident after further evaluation of the impact of occupational exposures (e.g., specific inhalation challenge).

A) Verification of asthma diagnosis

Diagnosis of occupational asthma does not differ from other asthma diagnostics. Asthma-like symptoms (e.g., periodic nocturnal cough, wheezing, chest tightness, and shortness of breath) are important for the diagnosis, but must always be supported by lung function test and evaluation of sensitization. It is important, to document asthma with one or more of the following tests: daily monitoring of FEV_1 or PEF, reversibility with bronchodilator and/or corticosteroids, or unspecific bronchial provocation with e.g., physical exercise, methacholine or mannitol, or to measure NO in expirated air, which is usually elevated in asthma patients.

B) Verification that asthma is caused by occupational exposures

To assess whether a patient's asthma is caused by an occupational exposure, the triggering exposure must be identified. The criteria for causality between the exposure and asthma comprise four questions: 1) Is there sufficient evidence that indicate that the exposure of interest can cause asthma (the evidence), 2) Is the patients type and amount of exposure able to cause asthma (exposure assessment), 3) Is there a temporal relation between exposure and onset of asthma (temporal coherence), and 4) Are there other competing reasons that are more important than the occupational sensitizing exposure.[24]

From the patient history, information about the patient's job, symptoms in relation to exposure (e.g., time of onset of symptoms, fewer/no symptoms in periods off work) can be obtained. If the history suggests asthma caused by occupational sensitizing exposures, one or more of the following tests are suggested:

- Peak flow monitoring (PEF) or FEV_1 measurements 3-5 weeks at least 5 times/day during the person's waking hours both during work and work-free periods. The use of asthma medication is

recorded simultaneously. There are freely available registration systems e.g., http://www.occupationalasthma.com/.

- Measurement of nonspecific bronchial hyperreactivity during work and work-free periods to detect any differences.
- Workplace challenge: FEV_1 is measured several times before, during, and after a work day.
- Skin prick test, specific IgE meaurements, histamine release tests and/or basophil activation test towards suspected sensitizing exposures at the workplace. In the case of HMW exposures, it may sometimes be appropriate to perform skin prick tests with materials from the workplace.
- Finally, sensitization to common inhalation sensitizing exposures is investigated, as atopy is a risk factor for occupational IgE-mediated asthma.

Specific inhalation challenge (SIC) – when?

If the causal relation is uncertain, and a precise diagnosis is important for the work prognosis of the patient, it may be relevant to perform SIC.[25, 26] Indication for SIC is more frequent, when patients are exposed to LMW exposures where skin prick test and specific IgE are not usually available. The patient is exposed to the suspected occupational exposure at controlled conditions close to an acute emergency department. Currently, SIC is performed at the three allergy centers in Denmark.

Evaluation of the quality of SIC

To assess whether SIC supports a causal relationship it is important to ask the following questions: A) Did the SIC use realistic exposure levels, B) Did the SIC include varying exposure level or varying exposure times to assess the dose-response relation and possible threshold level, C) Did the SIC includes a relevant negative control, and, and D) Was the patient blinded for exposure status (negative control or active exposure). The more affirmative answers to the above questions, the greater confidence one can have for a given positive provocation to reflect a causal link between exposure and asthma.

5. DISCUSSION

5.1 Main results

In *study I,* we found strong evidence of a relation for main group of wood dusts, and moderate evidence for the main groups of mites and fish. For subgroups/specific exposures, we found strong evidence for exposure to various laboratory animals, while moderate evidence was found for 55 subgroups/specific exposures (table 2, page 9).

In *study II*, we upgraded main groups of crustaceans and enzymes to moderate evidence. For subgroups/specific exposures, we upgraded pesticides, cleaning agents such as chloramine and disinfection products, and an unspecified group of other chemicals such as acrylates to moderate evidence.

Study I and II: When combining the results from our overview (study I) and systematic review (study II), we found strong evidence of a relation for main groups of wood dust, and moderate evidence for main groups of mites, fish, crustaceans, and enzymes. For subgroups/specific exposures, we found strong evidence for exposure to various laboratory animals, while moderate evidence was found for 60 subgroups/specific exposures (table 3, page 11).

In *study III*, we outlined guidelines for good clinical evaluation of patients with asthma suspected to be caused by occupational sensitizing exposures. In persons with suspected occupational athma, the key issue is to investigate the relation between the occupational sensitizing exposure under suspicion and the asthma disease. This includes the patient history, repeated lung function tests (e.g., FEV_1, PEF) at home and at work, an allergological evaluation with skin prick test, specific IgE measurement, histamine release test, and/or basophil activation test. Sometimes a specific inhalation challenge test with the suspected sensitizing exposure is needed.[19, 20]

5.2 Methodological considerations

Study I: Strengths of this overview were the systematic literature search performed in several databases, and that the exclusion of studies, quality assessment, and evaluation of the strength of evidence of a relation were performed independently by two reviewers. Data extraction was performed independently by two reviewers for 25 % of the included systematic reviews, which

showed good correlation. Due to the overview design, original studies might have been included in more than one review, and therefore weighted more when evaluating the relations. However, only few exposures were studied in more than one review (table 3). We did not include a large number of narrative reviews to avoid study selection bias and bias due to the authors´ subjective opinions. A potential limitation of the study was that the whole area of grey literature (e.g., reports or other not peer reviewed literature) was not included. We expected that articles with high scientific quality and therefore the most informative studies to be published in peer review journals, and therefore we do not expect that the exclusion of grey literature have influenced our conclusions.

The strength of relatin for a potential occupational sensitizing exposure was based on both the quantity and the quality of the included reviews. Of the 22 reviews, only three reviews were rated high. Exposures frequently studied obtained higher levels of evidence (e.g., methylene diphenyl-di-isocyanate). We did not review the original studies included in each of the reviews, but evaluated the evidence of relation based on the review conclusion and quality. The overall confidence in the study results was assessed subjectively based on AMSTAR 2. We especially emphasized criteria related to the literature search, study selection, assessment of risk of bias, and whether the authors accounted for risk of bias when evaluating the confidence in the results of the review.
In order to be comprehensive we included reviews where both adults and children were included as well as studies where the exposure were domestic, as long as the same exposure is also known as an occupational exposure (e.g., paint and pesticide exposure). It can be argued that the circumstances can be different for domestic exposures and occupational exposures (e.g., exposure more hours/week, higher or lower exposure levels), but still we regarded the information useful. The original studies in each systematic review could include epidemiological studies and/or clinical studies. A large proportion of the included studies were case studies, which in general is regarded as low evidence. But particular for asthma, case studies with good quality specific inhalation challenges can be regarded as an experiment without significant confounder issues and with a high quality of both exposure and outcome data.

Study II: The strengths and limitations of study II was almost similar to study I. Due to resource issues, we did not include all potential occupational sensitizing exposures classified as having limited or no evidence from our overview. We used specific criteria for including exposures, namely frequent potential occupational sensitizing exposures, suspected low molecular weight

exposures, and exposures which are not considered well known causes of asthma. We prioritized frequently used potential sensitizing exposures due the potential larger impact of preventive measures. We prioritized LMW exposures due to the less well known mechanisms and diagnostic tools of those agents. Finally, we focused on exposures currently debated among clinicians and researchers, for example epoxy resins and pesticides. Some of the main groups (e.g., metal) included heterogeneous exposures (e.g., metal working fluids). We included these heterogeneous exposures in order to be as comprehensive as possible. In order to disentangle the effect of specific cleaning agents, we decided to include cleaning agents under other chemicals, even though moderate evidence for unspecific cleaning agents was documented in the overview (study I). As in the overview, we also included clinical studies. Seventeen out of the 37 included studies were case-studies; of which five were rated high. As discussed in above, case studies are still an important source of information and add substantially to the evidence for most exposures.

In earlier risk of bias tools and quality of evidence tools, case studies are regarded as low evidence. But as described previously, case reports or case series including SIC can be regarded as an experiment. Therefore, we developed a new tool in order to judge observational studies and case studies together as seen in appendix 4 (paper II). The tool a priory did not give preferences to observational studies vs case or case series studies. We anticipate this tool to be useful in future reviews on studies dealing with risk factors for asthma.

Study III: The outlined guidelines for good clinical evaluation of patients with asthma suspected to be caused by occupational sensitizing exposures was conducted by clinicians and scientist within asthma and occupational medicine with several years of experience in the field. The guidelines followed the gold standard of asthma evaluation as described by National evaluations of asthma evaluation and by the Danish Society for respiratory Medicine and Danish Society for occupational and Environmental Medicine adherent with international Guidelines.[2]

5.3 Discussion of results

Study I: Our overview clarifies the level of evidence and uncovers gaps in systematic knowledge of the relation between potential occupational sensitizing exposures and asthma. The overlap between this overview and the comprehensive systematic review by Baur et. al. (2014)[15] is substantial and is

not surprising. Of note we found strong evidence of relation between asthma and the main group of wood dust, and moderate evidence for main groups of mites and fish, which was not evaluated in Baur et al. (2014).[15] We also found moderate evidence for 55 other subgroups/specific exposures compared to 36 exposures documented by Baur. This was mainly due to new studies conducted after 2011, when Baur performed his literature search.[15] We did not find clear evidence of relations with asthma for many animals and specific enzymes regarding well known causes of asthma (for example mice and proteolytic enzymes). An obvious reason could be that researchers have not prioritized performing systematic reviews on accepted risk factors.

We excluded reviews on exposures known to be irritants without any suspicion of a specific immunological mechanism, e.g., chlorine and ammonia. On the other hand, we included main and subgroup/specific exposures in order to be as comprehensive as possible at the expense of also including non-sensitizing exposures in our overview, so even though the purpose was to study potential occupational sensitizing exposures, the overview to some extends also deals with irritants without any specific mechanism of action. However, we did include exposures with partly nonspecific and irritative mechanisms, for example wood dust, isocyanates and cleaning agents, and we expect that some of the identified relations are based on non-specific mechanisms. By applying a structure with broad main groups as well as subgroups/specific exposure we aimed to be both comprehensive as well as transparent in our evaluations.

Study II: Even though the quality of the included studies was diverse ranging from low to high, we were able to upgrade the evidence level for more potential occupational sensitizing exposures, underlining the advantages of a systematic approach. At first sight, it is unexpected that the evidence for mammals was limited/contradictory. Due to high evidence in our overview for cow and rat sensitizing exposures they were not included in this review. Furthermore, sensitizing exposures well known to cause asthma for example from cats and dogs, are seldom investigated in occupational studies. So the limited evidence reflects relatively few studies on more or less specific mammals. Still it should be acknowledged that numerous animal proteins have the capacity to cause IgE-mediated allergy and eventually to cause asthma.

5.4 Perspectives

Identification of exposures in this reference document might help primary care physicians and occupational physicians in diagnosis/management of workers suffering from asthma and to prevent asthma in occupational settings. In future studies it is important to focus on exposure levels and exposure-response relations in order to perform specific and efficient prevention at the workplaces. Currently, specific occupational exposure limits are not available for occupational sensitizing exposures, but for some few exposures, for example specific enzymes,[27] data are available for setting health recommendations based occupational exposure limits. It is important to get access to similar knowledge for other exposures.

5.5 Conclusion and deliverables

The reference document summarizes the current level of evidence of the relation between occupational sensitizing exposures and asthma. We found strong evidence of a relation for main groups of wood dust, and moderate evidence for main groups of mites, fish, crustaceans, and enzymes. For subgroups/specific exposures, strong evidence was found for exposure to various laboratory animals, while moderate evidence was found for 60 subgroups/specific exposures (table 3, page 11). We updated clinical guidelines with the evidence found in this reference document.

The achieved documentation is summarised in Danish and English tables.

6. ENGLISH SUMMARY

Background

Asthma is a chronic inflammatory disorder of the airways, which is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. The relation between occupational sensitizing exposures and asthma has been studied in numerous studies and include a large number of exposures. In a comprehensive review of 372 potential occupational sensitizing exposures, Baur *et. al.* (2014) found strong evidence of a relation for exposure to various laboratory animals and moderate evidence for 35 exposures, limited or very limited/contradictive evidence for 61 exposures, and no scientific evidence for the remaining exposures. New occupational sensitizing exposures are continually being reported; therefore, a systematic update of the current list of occupational sensitizing exposures together with the level of evidence for each exposure may assist companies and regulating bodies preventing asthma and physicians in diagnosing and managing workers suffering from occupational asthma. The aim of this reference document was to examine the relation between potential occupational sensitizing exposures and asthma (study I and II), and to generate guidelines for clinical evaluation of patients with asthma suspected to be caused by occupational exposures (study III).

Materials and methods

In *study I*, we conducted an overview of systematic reviews with a systematic literature search performed in four databases for peer-reviewed systematic reviews published before 29th of August 2017. Eligible criteria for study inclusion comprised a population in or above working age, sensitizing exposures present in the occupational environment, a measure of association between exposures and asthma, and outcome defined as asthma. Two reviewers selected studies, extracted study data, assessed study quality, evaluated the overall confidence in study results, and the strength of evidence for main groups and subgroups/specific exposures.

In *study II*, we conducted a systematic review. The literature search was performed in three databases for peer-reviewed studies published between 1st of July 2011 and 7th of June 2019. Based on study I, we selected 10 potential occupational sensitizing exposures with no to limited evidence of a relation. Two reviewers selected studies, extracted study data, assessed study quality, evaluated the overall confidence in study results, and the strength of evidence for main groups and subgroups/specific exposures.

In *study III,* we conducted a narrative review performed by Danish physicians and scientist with expertise in asthma and occupational medicine.

Results

In *study I,* a total of 22 systematic reviews were included, comprising 1189 studies and 486 potentially occupational sensitizing exposures. The overall confidence in study results was rated high in three reviews, moderate in four reviews, and low in 14 reviews. We found strong evidence of a relation for the main group of wood dust, and moderate evidence for mites and fish. For subgroups/specific exposures, we found strong evidence for exposure to laboratory animals, while moderate evidence was found for 55 subgroups/specific exposures varying from animals, plants, "moulds, fungi and yeast", enzymes, drugs, metals, dyes, isocyanates, anhydrides, and other chemical compounds.

In *study II*, a total of 37 studies were included, which covered seven out of 10 selected potential occupational sensitizing exposures; no studies were found for amines, anhydrides, and molluscs. For the seven studied exposures, we upgraded main groups of crustaceans and enzymes to moderate evidence. For subgroups/specific exposures, we upgraded pesticides, cleaning agents such as chloramine and disinfection products, and an unspecified group of other chemical such as acrylates to moderate evidence.

In *study III*, we outlined that the clinical evaluation of occupational asthma typically includes a combination of patient history, repeated lung function testing (e.g., FEV_1, peak expiratory flow) at home and at work, an allergological evaluation with skin prick test, specific IgE, histamine release test and/or basophil activation test. Sometimes a specific inhalation challenge test with the suspected allergen is needed.

Conclusion

This reference document summarizes the current level of evidence of the relation between potential occupational sensitizing exposures and asthma. We found strong evidence of a relation for main groups of wood dust, and moderate evidence for mites, fish, crustaceans, and enzymes. For subgroups/specific exposures, strong evidence was found for exposure to various laboratory animals, while moderate evidence was found for 60 subgroups/specific exposures. We specified guidelines for clinical evaluation of patients with asthma suspected to be caused by occupational sensitizing exposures.

7. DANSK RESUME

Baggrund og formål

Astma er en sygdom med anfaldvis hoste, åndenød, og pibende hvæsende vejrtrækning. Patologisk er astma karakteriseret ved variabel luftvejsobstruktion, re-modellering af bronkier og bronkioler, samt kronisk bronkial inflammation.[2] Sygdommen optræder oftest tidligt i barndommen, men kan debutere hele livet. Prævalensen af forældrerapporteret læge-diagnosticeret astma blandt 7 årige børn i Danmark er omkring 12 %.[4] Incidensen af astma defineret ud fra indlæggelser eller brug af astmamedicin blandt 5-14 årige børn bosiddende i Danmark er ca. 18/1000 personår.[5] Hos voksne er prævalensen for selvrapporteret astma blandt voksne 6 % i Danmark, imens den i de nordiske lande er 5-10 %.[7] Incidensen af selvrapporteret astma blandt voksne i Norden er betydeligt lavere (ca. 2/1000 personår).[8]

Sammenhængen mellem potentielle arbejdsrelaterede sensibiliserende eksponeringer og astma er blevet undersøgt i adskillige studier og inkluderer et stort antal eksponeringer. I et omfattede systematisk review, undersøgte Baur et. al. (2014) evidensen for en sammenhæng mellem 372 potentielle arbejdsrelaterede sensibiliserende eksponeringer og astma. Dette review viste, at der er stærk evidens for en sammenhæng for forskellige laboratoriedyr og moderate evidens for 35 eksponeringer. For de resterende eksponeringer fandt studiet ingen eller begrænset evidens. Der rapporteres løbende nye potentielle arbejdsrelaterede sensibiliserede eksponeringer. Derfor kan en systematisk opdatering af den aktuelle liste af arbejdsrelaterede sensibiliserende eksponeringer samt graden af evidens for en sammenhæng for den enkelte eksponering hjælpe virksomheder og regulerende organer i at forebygge astma samt læger i diagnosticeringen og reguleringen af arbejdsrelaterede astma.

Formålet med dette referencedokument er, at præsentere og vurdere den videnskabelige dokumentation for en sammenhæng mellem potentielle arbejdsrelaterede sensibiliserende eksponeringer og astma (studie I-II), og at udarbejde guidelines for klinisk vurdering af personer, som mistænkes for astma forårsaget af potentielle arbejdsrelaterede sensibiliserende eksponeringer (studie III).

Materiale og metode

Referencedokumentet omfatter tre studier hhv. et overview af systematiske review (studie I), systematisk review (studie II) og et narrativ review (studie III). Projektprotokollen for studierne er registreret i PROSPERO.

Studie I blev udarbejdet som et overview af systematiske review. Der blev foretaget en systematisk litteratursøgning i samarbejde med en bibliotekar i henholdsvis PubMed/MEDLINE, Embase og Web of Science (WoS), og Cochrane for videnskabelige artikler publiceret før den 29. august 2017. Potentielle relevante artikler omfattede systematiske reviews, som opfyldte a priori-definerede PECO-kriterier (Population, Exposure, Comparison, Outcome). Disse kriterier inkluderede personer i eller over den arbejdsdygtige alder, potentielle arbejdsrelaterede sensibiliserende eksponeringer, en vurdering af sammenhængen mellem potentielle arbejdsrelaterede sensibiliserende eksponeringer og astma, samt udfald defineret som astma. Efter litteratursøgningen blev potentielle relevante artikler overført til online programmet Covidence. I Covidence blev duplikater ekskluderet, hvorefter udvælgelsen af relevante artikler blev foretaget i tre trin hhv. titel screening, abstrakt screening og gennemlæsning af hele artiklen. Denne proces blev foretaget af to af projektgruppens medlemmer; uoverensstemmelse blev løst ved konsensus. Efter udvælgelse af relevante artikler, blev oplysninger om studiernes design, population, udfald og eksponering mm ekstraheret til tabeller, og der blev foretaget en kvalitetsvurdering af hvert studie vha. AMSTAR 2, som indeholder 16 spørgsmål til vurdering af den metodologiske kvalitet i systematisk reviews. Associationen mellem potentielle arbejdsrelaterede sensibiliserende eksponeringer og astma blev præsenteret i tabeller, og graden af evidens for en associationen blev vurderet vha. "Royal College of General Practitioners' system" (RCGP). Ovennævnte processer/trin blev foretaget af to af projektgruppens medlemmer.

Studie II blev udarbejdet som et systematiske review. PECO-kriterierne var identisk med kriterierne for studie I, dog udvalgtes 10 potentielle arbejdsrelaterede sensibiliserende eksponeringer med ingen eller begrænset evidens baseret på vores overview af systematiske reviews. I samarbejde med en bibliotekar blev litteratursøgningen foretaget i 3 databaser for peer-review studier publiceret mellem 1. januar 2011 og 7. juni 2019; litteratursøgningen i Baur et. al. (2014) blev foretaget juli, 2011. I Covidence blev duplikater og artikler publiceret før 1. juli 2011 ekskluderet, hvorefter udvælgelsen af relevante artikler blev foretaget i to trin hhv. titel/abstract screening og

gennemlæsning af hele artiklen. Denne proces blev foretaget af to af projektgruppens medlemmer; uoverensstemmelse blev løst ved konsensus. For hver artikel ekstraheredes oplysninger om studie-design, population, eksponering og udfald mm. Studiernes kvalitet blev vurderet ud fra en kvalitetsvurderingsmodel udarbejdet til dette formål, imens graden af evidens for en sammenhæng blev vurderet via RCGP. Ovennævnte processer/trin blev foretaget af to af projektgruppens medlemmer.

Studie III blev udarbejdet som et narrative review af arbejdsmediciner og forskere med særlig ekspertise inden for lungesygdomme og arbejdsmedicin.

Resultater

Studie I omfattede 22 systematiske review, hvilket indeholdt 1189 studier og 486 potentielle arbejdsrelaterede sensibiliserende eksponeringer. Baseret på kvalitetsvurderingen af de 22 studier, blev tiltroen til studiernes konklusion vurderet høj i 3 reviews, moderat i 5 reviews, og lav i 14 reviews. Resultaterne viste stærk evidens for en sammenhæng for hovedgruppen træstøv samt moderat evidens for mider og fisk. For subgrupper/specifikke eksponeringer, viste resultaterne stærk evidens for eksponering for forskellige laboratoriedyr, samt moderat evidens for 55 forskellige subgrupper/specifikke eksponeringer.

Studie II omfattede 37 studier, hvilket inkluderede syv af de 10 udvalgte potentielle arbejdsrelaterende sensibiliserede eksponeringer. Baseret på kvalitetsvurderingen af de 22 studier, blev tiltroen til studiernes konklusion vurderet høj i 5 reviews, moderat i 13 reviews, og lav i 14 reviews. Der forelå ingen studier for aminer, anhydrider og bløddyr. For de syv studerede potentielle arbejdsrelaterede sensibiliserende eksponeringer var der evidens for at opgradere hovedgrupper af kredsdyr og enzymer til moderat evidens. For subgrupper/specifikke eksponeringer, blev pesticider, rengøringsmidler såsom kloramine og disinfektionsprodukter, samt en uspecifik gruppe af øvrige kemikalier opgraderet såsom acrylates til moderat evidens.

Baseret på studie I og II, foreligger der stærk evidens for hovedgruppen træstøv samt moderat evidens for mider, fisk, krebsdyr og enzymer. For subgrupper/specifikke eksponeringer foreligger der stærk evidens for eksponering for laboratoriedyr, imens der foreligger moderat evidens for 60 subgrupper/specifikke eksponeringer.

I studie III tydeliggøres at diagnostikken af arbejdsbetinget astma ikke adskiller sig fra anden astma diagnostik. Ved optagelse af anamnese indhentes oplysninger om erhverv, mulige eksponeringer, og arbejdsrelation (tidspunkt for debut af symptomer, færre/ingen symptomer i friperioder). Hvis der ud fra anamnesen fortsat er mistanke om astma forårsaget af eksponeringer på arbejdspladsen suppleres med en eller flere undersøgelser for at afdække sammenhængen mellem astma og arbejdsrelaterede sensibiliserende eksponeringer: 1) Peak flow monitorering og FEV_1 måling: Foregår oftest via en arbejdsmedicinsk klinik. Der gennemføres typisk 3-5 ugers PEF og FEV_1-måling på faste tidspunkter mindst 5 gange/dag i personens vågne timer både i arbejds- og arbejdsfri perioder, 2) Måling af uspecifik bronkial hyperreaktivitet i arbejds- og arbejdsfri perioder for at påvise en evt. forskel, 3) Priktest, specifikt IgE, histamine release test eller basofil aktiveringstest overfor mistænkte sensibiliserende eksponeringer på arbejdspladsen. Ved høj-molekylære sensibiliserende eksponeringer kan det af og til være hensigtsmæssigt at prikteste med materiale fra arbejdspladsen, ligesom der kan sendes materiale fra arbejdspladsen til Reference Laboratoriet (www.reflab.dk) med henblik på histamin release test. Hvis den kausale sammenhæng er usikker, kan der suppleres med specifik inhalations provokation (specific inhalation challange, SIC)

Konklusion

Baseret på et overview af systematiske reviews samt et systematisk review om potentielle sensibiliserende eksponeringer foreligger der stærk evidens for en sammenhæng mellem hovedgruppen træstøv og astma, samt moderat evidens for mider, fisk, krebsdyr og enzymer. For subgrupper/specifikke eksponeringer foreligger der stærk evidens for eksponering for laboratoriedyr samt moderat evidens for 60 subgrupper/specifikke eksponeringer. Referencedokumentet indeholder guidelines for klinisk vurdering af personer, som mistænkes for astma forårsaget af potentielle arbejdsrelaterede sensibiliserende eksponeringer.

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9. ORIGINAL PAPERS

Paper I To conduct an overview of systematic reviews to summarize the existing evidence of the relation between potential occupational sensitizing exposures and the development of asthma in the working population.

Paper II To conduct a systematic review of the relation between asthma and 10 potential occupational sensitizing exposures classified as having no or limited evidence in the overview of systematic reviews.

Paper III To generate guidelines for clinical evaluation of patients with asthma suspected to be caused by occupational sensitizing exposures.

PAPER I

The relation between potential occupational sensitizing exposures and asthma: an overview of systematic reviews

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ABSTRACT

Introduction: We conducted an overview of systematic reviews summarizing the existing scientific evidence of the relation between potential occupational sensitizing exposures and asthma.

Materials and methods: A systematic literature search in four databases was conducted for peer-reviewed systematic reviews published before the 29th of august 2017. Eligible criteria for study inclusion comprised a population in or above working age, potential sensitizing exposures present in the occupational environment, outcome defined as asthma, and a measure of association between the potential sensitizing exposure and asthma. Two reviewers selected studies, extracted study data, assessed study quality, evaluated the overall confidence in study results and the strength of evidence of relation for main groups and subgroups/specific exposures.

Results: A total of 22 systematic reviews were included, comprising 1189 studies and 486 potential occupational sensitizing exposures. The overall confidence in study results was considered high in three reviews, moderate in four reviews, and low in 14 reviews. We found strong evidence of a relation for the main group of wood dusts, and moderate evidence for the main groups of mites and fish. For subgroups/specific exposures, we found strong evidence for work tasks including exposure to laboratory animals, whereas moderate evidence was found for 55 subgroups/specific exposures varying from animals, plants, "moulds, fungi and yeast", enzymes, drugs, metals, dyes, isocyanates, anhydrides, and other chemical compounds.

Conclusion: The present overview provides an updated list of potential occupational sensitizing exposures able to cause asthma together with the level of evidence.

BACKGROUND

It is estimated that approximately 300 million people worldwide suffer from asthma.[1] Among countries, the prevalence proportion of clinically assessed asthma ranges between 1 % and 21 % in the general adult population.[2] Within countries, the incidence proportion varies according to occupational groups, where professional, clerical and administration (1.8 %) are considered low risk groups, while nurses (4.8 %), wood workers (3.9 %), printers (3.6 %), cleaners and care takers (3.4 %), and agricultural and forestry workers (3.1 %) are considered high risk groups.[3]

Approximately 10-15 % of adult asthma can be attributed to occupational irritants and sensitizing exposures.[4, 5] Sensitizing exposures can be divided into high-molecular-weight (HMW) exposures - primarily proteins with plant and animal origin, and low-molecular-weight (LMW) exposures e.g., metals and chemicals. HMW exposures and a few LMW exposures (e.g., platinum salts, reactive dyes, acid anhydrides, sulfonechloramide, and some wood species) act through an IgE-mediated mechanism. The immunological mechanisms underlying the effects of most LMW exposures (e.g., isocyanates, persulphate salts, aldehydes, and wood dusts) have not been fully characterized.[6, 7] In addition, several exposures can act both as sensitizers and irritants (e.g., isocyanates, wood dust).

Several hundred potential occupational sensitizing exposures have been suspected to cause asthma.[9, 10] In a comprehensive review of 865 original papers of 372 potential occupational sensitizing exposures, Baur *et. al.* (2014)[11] found strong evidence of a relation for exposure to various laboratory animals, moderate evidence for 35 exposures, limited or very limited or contradictory evidence for 61 exposures, and no evidence for the remaining exposures. New sensitizing exposures are continually being reported; therefore, a systematic update of the current list of sensitizing exposures together with the level of evidence for each exposure may assist companies,

Occupational Health and Safety Institutions, and regulating bodies in preventing asthma. An updated list may also help physicians in diagnosing and managing workers suffering from occupational asthma.

The National Board of Industrial Injuries and the Occupational Diseases Committee in Denmark requested a detailed scientific reference document of the causality between potential occupational sensitizing exposures and the development of asthma. To summarize the existing knowledge and synthesize the evidence gained from the large number of exposures reported in numerous studies, an overview of systematic reviews is a logical choice. The aim of this study was to conduct an overview of systematic reviews to summarize the existing evidence of the relation between potential occupational sensitizing exposures and the development of asthma in the working population.

MATERIALS AND METHODS

Protocol and registration

The study was conducted as an overview of systematic reviews, which followed the specific guidelines for preparation and quality approval provided by the Danish Work Environment Fund, supplemented by guidelines from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[12] The study protocol was registered in PROSPERO (CRD42017057014).

Literature search, eligible criteria and exclusion of studies

We performed a systematic literature search for peer-reviewed systematic reviews published before the 29th of august 2017 based on definitions described in our PECO (Population, Exposure, Comparison, Outcome) (appendix 1)). The search was conducted by AD, VS, and HK in collaboration with a librarian using the following international electronic databases: The National Library of Medicine (MEDLINE/PubMed), Embase, Web of Science (WoS), and Cochrane. The full literature search string for PubMed is presented in appendix 2.

All potentially relevant articles were transferred to the online software tool Covidence (https://www.covidence.org). Duplicate articles were excluded, and identification of relevant articles was performed in three steeps; title screening, abstract screening, and full paper reading. Throughout the selection procedure, evaluation was done independently by two reviewers (AD and VS), and in case of disagreement the article was moved to the next step (i.e., abstract screening or full paper reading). Disagreement after full paper reading was solved by consensus. Appendix 3 lists criteria for study exclusion for each of the three steps. We only included systematic reviews, defined as comprising a systematic literature search performed in one or more international electronic databases. Original studies in a systematic review could comprise epidemiological (e.g., cross-sectional, case-control, and cohort studies) and/or clinical studies (e.g., case-reports and case-series). The study population was restricted to adults in or above working age, but in order to be comprehensive we did not exclude studies which included both adults and children. We also included studies of exposure groups, which could include both sensitizers and irritants (e.g., cleaning agents), and domestic studies if they provided information about exposures also occurring at work places (e.g., paint and cleaning agents). The literature search was extended by screening the reference lists of all reviews included.

Data extraction and methodological quality assessment of each systematic review

From each included systematic review, we extracted core study information (e.g., author, searched databases, included number of studies, study designs, population, outcome, and exposure), measure of association, and study conclusion of the relation between potential occupational sensitizing exposures and asthma. For approximately 25 % of the included reviews, data extraction was performed independently by two reviewers (AD and VS), which was then compared and discussed by the two reviewers. For the remaining reviews, study data was extracted by one reviewer (AD) and quality check by another reviewer (VS).

The methodological quality of each included review was assessed independently by two reviewers (AD, VS, or HK) using the quality assessment tool AMSTAR 2; a 16-item tool designed to appraise the methodological quality of systematic reviews.[13] Most items were scored "Yes" or "No", while some items could be answered "Partial yes" or "No meta-analysis conducted". Based on AMSTAR 2, the overall confidence of the results of each review was rated "Critically low", "Low", "Moderate", or "High". Disagreement on item quality and overall confidence was discussed among the two reviewers and resolved by consensus. Blinding for authorships was not possible since several reviews were well known to the reviewing authors. We pilot tested the methodological quality assessment of five systematic reviews to ensure that criteria were applied consistently, and that consensus could be reached. The source of funding for each of the included reviews was evaluated but not reported.

Quality of evidence of the relation between sensitizing exposures and asthma across reviews

We divided the exposures into main groups according to the grouping performed by Baur et. al. (2014)[11]. We included main and subgroups in order to be as comprehensive as possible. Based on

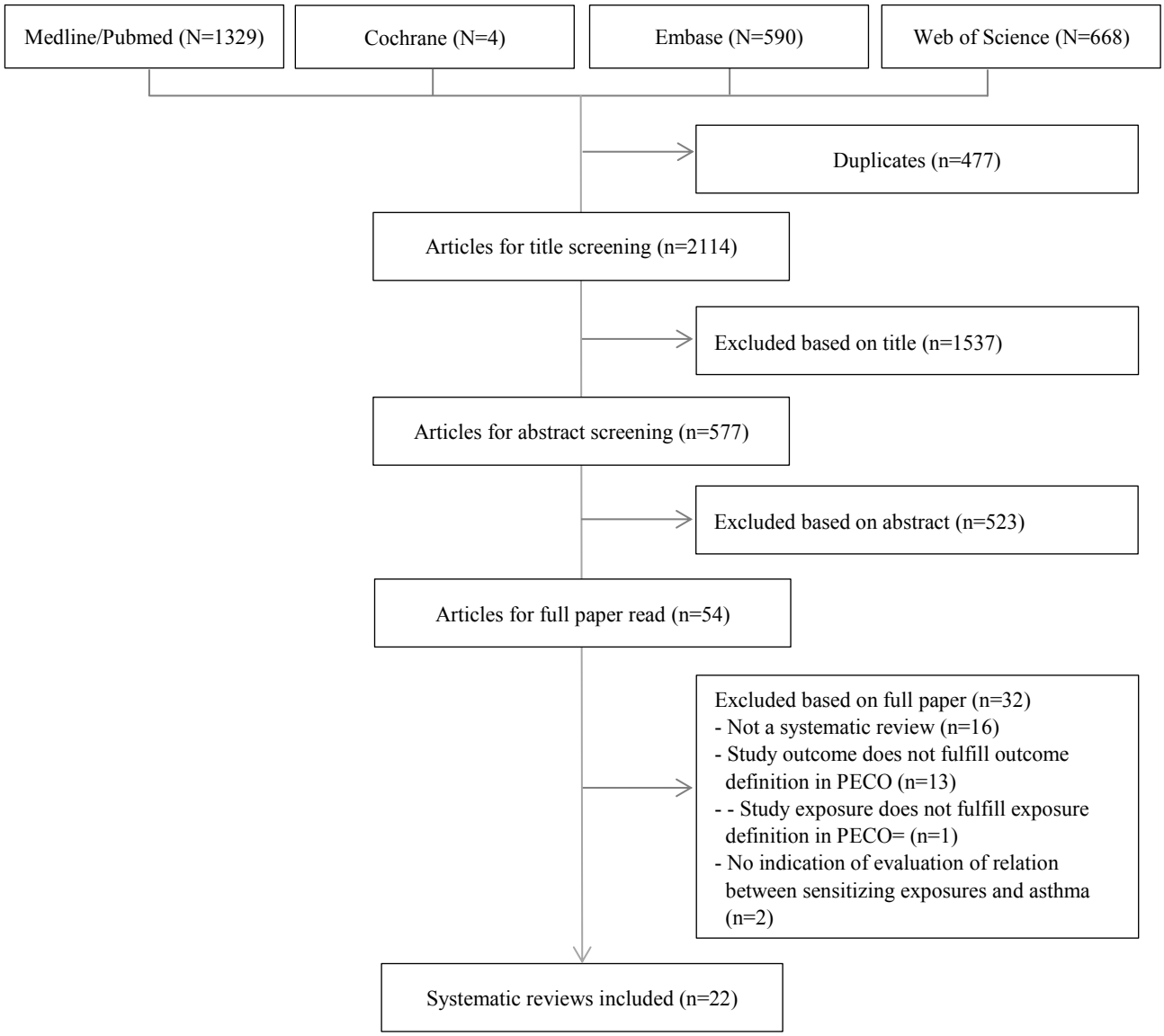
the included reviews, the quality of evidence of the relation between asthma and main exposure groups (e.g., mammals) and subgroups/specific exposures (e.g., bats, cows, deer, elks) was assessed by two reviewers (AD and VS) using a modification of the Royal College of General Practitioners' (RCGP) system of the British Occupational Health Research Foundation (appendix 4-5).[11, 14]

RESULTS

Literature search and exclusion of studies

Figure 1 presents a flow chart of the literature search and exclusion of articles. The literature search included 2591 articles with 477 duplicates, providing 2114 potentially relevant articles. After title screening, 1537 articles were excluded, and 577 articles were moved to abstract screening (disagreement occurred in 200 out of 2114 cases). We excluded additional 523 articles after abstract screening, providing 54 articles for full paper reading (disagreement occurred in 18 out of 523 cases). After full paper reading, a total of 22 systematic reviews were included in the overview (disagreement occurred in five out of 54 cases). Appendix 6 lists excluded articles and the reason for their exclusion.

Figure 1. Flow chart of the literature search and exclusion of studies



Study characteristic and quality

Table 1 summarizes study characteristic of the 22 included systematic reviews, which covered 1189 studies and 486 potential occupational sensitizing exposures. The 1189 studies included epidemiological studies (i.e., cross-sectional, case-control, cohort studies, and reviews) and clinical studies (i.e., case-reports and case-series). The comparison between data extraction for the two reviewers was subjectively rated high.

Table 2 presents the quality assessment of the 22 reviews. The overall confidence in review results was rated "high" for three reviews, "moderate" for five reviews, and "low" for 14 reviews. The most frequent quality items scored "no" were the "Did the review authors provide a list of excluded studies and justified the exclusions?" and "Did the review author report on the source of funding for the studies included in the review?"

Quality of evidence of a relation between occupational sensitizing exposures and asthma

Table 3 presents the relation between potential occupational sensitizing exposures and asthma, and the quality of evidence of the relation for main groups and subgroups/specific exposures. The results for main groups are presented in total, whereas the relation for subgroups/specific exposures is presented if the relation is moderate or strong. The comparison between data extraction for the two reviewers was subjectively rated high.

ANIMALS

Crustaceans: Crustaceans were studied in one review, including 11 studies of four crustaceans.[11] The review found no evidence of a relation for lobsters, limited/contradictory evidence for shrimps, and moderate evidence for two crustaceans (i.e., prawns and snow crabs). Our overall confidence in review results was considered moderate. Based on the existing review, limited/contradictory evidence was identified for the main group of crustaceans, while moderate evidence was identified for prawns and snow crabs.

Insects: Insects were studied in two reviews including 50 studies of 31 insects.[11, 15] One moderate quality-rated review, found no evidence for 23 insects, limited or very limited/contradictory evidence for five insects (i.e., flour moth, live fish bait, mealworm, non-biting midges, and screwworm fly), and moderate evidence for two insects (i.e., locust and silkworm).[11] A low quality-

rated review listed sludge worm (Tubifex tubifex) as a causative exposure.[14] Altogether, no evidence was identified for the main group of insects, but moderate evidence was identified for locust and silkworm.

Mites: Two reviews studied mites, which included 46 studies of six mites.[11, 15] One moderate quality-rated review found limited or very limited/contradictory evidence for two mites (i.e., house dust mites and poultry mites), and moderate evidence for three mites (i.e., predatory, spider, and storage mites),[11] while a low quality-rated review listed dust Tyrophagus putrescentia as a causative exposure.[15] Based on the existing reviews, we identified moderate evidence for the main group of mites and specifically for predatory, spider, and storage mites.

Fish: One moderate quality-rated review studied fish, which included seven studies of five fish.[11] The review found moderate evidence for all five fish (i.e., Atlantic salmon, seafood, fishmeal, trout, and turbot). Hence, we identified moderate evidence for the main group of fish and specifically for Atlantic salmon, seafood, fishmeal, trout, and turbot.

Mammals: One moderate quality-rated review of 38 studies including 14 mammals found no evidence for 10 mammals, limited or very limited/contradictory evidence for two mammals (i.e., black bats and mouse), and moderate evidence for two mammals (i.e., cows and rats).[11] Altogether, no evidence was identified for the main group of mammals, hence, we identified moderate evidence for cows and rats.

Animal products: One moderate quality-rated review of 22 studies found no evidence for eight out of nine animal products; egg proteins showed moderate association.[11] So no evidence was identified for the main group of animal products, but we identified moderate evidence for egg proteins.

PLANTS

Plants (excluding wood dust): Plants were studied in three reviews, which included 237 studies of 110 plants.[11, 15, 16] One moderate quality-rated review found no evidence for 84 plants, limited to very limited/contradictory evidence for 15 plants, while moderate evidence was found for six plants (i.e., latex, psyllium, coffee (raw), paprika, tobacco, and tea dust (various)).[11] One low quality-rated review concluded that textile fibers was related to asthma,[16] while another low quality-rated review listed orange tree aerollergen and orange zest as causative exposures.[14] Based on the existing reviews, we identified no evidence for the main group of plants, but moderate evidence for latex, psyllium, coffee (raw), paprika, tobacco, and tea dust (various).

Wood dust: Seven reviews included 156 studies of either main groups of wood dust (e.g. softwood, hardwood) or subgroups/specific wood dust (e.g., beech, cabreuva, and oak).[11, 15, 17-21] Six low to high quality-rated reviews found a relation for groups of wood dust,[15, 17-21] while a relation was found for western red cedar in two reviews with low to moderate quality rating.[11, 14] No evidence was found for more specific types of wood dust (n=38).[11] Based on the existing reviews, mainly including epidemiological studies, strong evidence was identified for the main group of wood dust, while moderate evidence was found for western red cedar.

FUNGI, MOULD, YEAST

Fungi, mould, yeast: Four low to strong quality-rated reviews studied fungi, mould, and yeast; 61 studies of 25 exposures.[11, 22-24] No evidence was found for 18 exposures, limited or very limited/contradictory evidence for two exposures (i.e., boletus edulis and Alternaria),[11] moderate evidence for *Aspergillus niger*,[11] while a relation was found for three exposures (i.e., *Aspergillus, Cladosporium*, and *Penicllium* species.[11, 15, 22] These associations were based on observational studies, susceptible individuals, and mainly domestic exposures among both children and adults.[22]

So even though strong evidence was identified for *Aspergillus, Cladosporium*, and *Penicllium* genera, we decided to downgrade to moderate evidence in this review where the main focus was occupational exposures. For the main group of fungi, mould, and yeast we identified no evidence.

ENZYMES

Enzymes were studied in two low-to-moderate quality-rated reviews including 88 studies of 41 enzymes.[11, 15] In one moderate quality-rated review, no evidence was found for 24 enzymes, limited or very limited/contractive evidence was found for 10 enzymes, and moderate evidence was found for five enzymes (i.e., a-amylase from aspergillus oryzae, detergent enzymes, papain, phytase from Aspergillus niger, and various enzymes from Bacillus subtilis).[11] In a low quality-rated review, three enzymes were listed as causative exposures (i.e., alfa-amylase termanyl, microbial transglutaminase, and savinase).[15] Based on the existing reviews, limited or contradictory evidence was found for the main group of enzymes; however moderate evidence was identified for a-amylase from aspergillus oryzae, detergent enzymes, papain, phytase from Aspergillus niger, and various enzymes from Bacillus subtilis.

BIOCIDES AND OTHER CHEMICALS:

Drugs: Drugs were studied in two reviews; 44 studies of 21 drugs.[11, 15] In a review with moderate quality, no evidence was found for 16 drugs, limited/contractive evidence was found for three drugs (i.e., cephalosporin, penicillines, and penylglycine acid chloride), while moderate evidence was found for opiates; no study conclusion was found for one drug.[11] A low quality-rated review, listed potassium tetrachloroplatinate as a causative exposure.[15] Based on the existing reviews, no evidence was identified for the main group of drugs, but moderate evidence was identified for opiates.

Metals: Metals were studied in one moderate quality-rated review; 30 studies of 14 metals.[11] No evidence was found for 12 metals, very limited/contractive evidence was found for chromium/nickel, and moderate evidence was found for platinum salts. Based on the existing review, no evidence was identified for the main group of metals; however, moderate evidence was identified for platinum salts.

Dyes: Two reviews included 18 studies of seven dyes.[11, 15] One moderate quality-rated study found no evidence for four dyes and moderate evidence for two dyes (i.e., carmine and reactive dyes),[11] while one low quality-rated review listed carmine red as a causative exposure.[15] Based on the reviews, we identified no evidence for the main group of dyes, but moderate evidence for carmine and reactive dyes.

Isocyanates: One moderate quality-rated review including 22 studies of six isocyanates found no evidence for two isocyanates (i.e., and 1,5-naphthalene diisocyante and triglycidyl isocyanurate), limited/contractive evidence for one isocyanate (i.e., hexamethylene diisocyanate), and moderate evidence for three isocyanates (i.e., toluene diisocyanates, methylene diphenyldiisocyanate (MDI), and various isocyantes (not specified)).[11] Based on the review, we found limited or contradictory evidence for the main group of isocyanates, but we identified moderate evidence for toluene diisocyanates, methylene diphenyldiisocyanate (MDI), and various other isocyanates not specified.

Anhydrides: One moderate quality-rated review included 14 studies of eight anhydrides.[11] No evidence was found for three anhydrides (Phthalic anhydride/chlorendic anhydride, Maleic anhydride, and various anhydrides), limited or very limited/contradictory evidence for four anhydrides (i.e., tetrachlorophthalic anhydride, methyl tetrachlorophthalic anhydride, hexahydrophthalic anhydride, and trimellicic anhydride), while moderate evidence was found for phthalic anhydride. Based on this review, we identified limited or contradictory evidence for the main group of anhydrides, but moderate evidence for phthalic anhydride.

Other chemical compounds: Eight low to moderate quality-rated reviews included 160 studies of 10 chemical compounds.[8, 11, 15, 25-29] Four reviews found a relation for cleaning products (i.e., cleaning spray, bleach, mixing products, disinfectants including glutaraldehyde, formaldehylde, chloamine-T, quanternary ammonium compounds),[8, 25, 26, 28] and one low quality-rated review listed acrylic resin, cyanoacrylate, and PVC powder as causative exposures.[15] Overall, we identified limited or contradictory evidence for the main group of other chemical compounds, but moderate evidence for the large and heterogeneous subgroup of cleaning products (i.e., cleaning spray, bleach, mixing products, glutaraldehyde, formaldehylde, chloamine-T, and quanternary ammonium compounds).

SENSITIZING EXPOSURES IN SPECIFIC OUUPATIONS/WORKSITES

Potential sensitizing exposures in different occupations/worksites have been studied in two reviews including 60 studies of farming, bakery, brewery, welding, and greenhouse workers.[11, 24] One moderate quality-rated review found no evidence for five exposures, limited or very limited/contradictory evidence for rye flour, moderate evidence for farming (i.e., animals, cereal, hay and straw, storage mites), bakery (i.e., flour, amylase, and storage mites), soybean (i.e., hulls, flour, and enzymes), and strong evidence for exposure to various laboratory animals.[11] A low quality-rated review found that exposure to dust, bacteria, allergens, fungi, and gases cause or exacerbate asthma in greenhouse workers.[24] Overall, we identified strong evidence for exposure to various laboratory animals, and moderate evidence for farming (i.e., animals, cereal, hay and straw, storage mites), bakery (i.e., flour, amylase, storage mites), and soybean (i.e., hulls, flour, and enzymes).

DISCUSSION

Main results

This overview included 22 systematic reviews, covering 1189 studies and 486 potential occupational sensitizing exposures. We found strong evidence of a relation for the main group of wood dust, and moderate evidence for main groups of mites and fish. For subgroups/specific exposures, strong evidence was found for work tasks including exposure to laboratory animals, while moderate evidence was found for 55 subgroups/specific exposures including *animals*; crustaceans (i.e., prawns, snow crabs), insects (i.e., locust, stilkworn), mites (i.e., predatory mites, spider mites, storage mites), fish (i.e., Atlantic salmon, seafood, fishmeal, trout, turbot), mammals (i.e., cows, rats), animal products (i.e., egg proteins), *plants*; (i.e., latex, psyllium, coffee raw, paprika, tobacco, various tea dust, western red cedar), *mould, fungi and yeast* (i.e., *Aspergillus, Cladosporium*, *Penicllium species*), *enzymes* (i.e., a-amylase from Aspergillus oryzae, detergent enzymes, papain, phytase from Aspergillus niger, various enzymes from Bacikkus subtilis), *drugs* (i.e., opiates), *metals* (i.e., platinum salts), *dyes* (i.e., carmine, reactive dyes), *isocyantes* (i.e., toluene diisocyanates, methylene diphenyl-diisocyante, various isocyanates), anhydrides (i.e., phthalic anhydride), other chemical compounds (i.e., cleaning products: cleaning spray, bleach, mixing products, glutaraldehyde, formaldehylde, chloamine-T, quanternary ammonium compounds), exposures in occupations/worksites (i.e., farming (animals, cereal, hay/straw, storage mites), bakery (flour, amylase, storage mites), and soybean (hulls, flour, enzymes).

Methodological considerations

Strengths of this overview were the systematic literature search performed in several databases, and that the exclusion of studies, methodological quality assessment, and evaluation of the strength of evidence of a relation were performed independently by two reviewers. Data extraction was

performed independently by two reviewers for 25 % of the included systematic reviews. Due to the overview design, original studies might have been included in more than one review, and therefore weighted more when evaluating the relation. However, only few exposures were studied in more than one review (table 3). We did not include a large number of narrative reviews to avoid study selection bias and bias due to the authors´ subjective opinions.

The strength of relation for an exposure was based on both the quantity and the quality of the included reviews. Of the 22 reviews, only three reviews were rated high. Exposures frequently studied obtained higher levels of evidence (e.g., methylene diphenyl-di-isocyanate). We did not review the original studies included in each of the systematic reviews, but evaluated the evidence of relation based on the review conclusion and quality. The overall confidence in the study results were assessed subjectively based on AMSTAR 2. We especially emphasized criteria related to the literature search, study selection, assessment of risk of bias, and whether the authors accounted for risk of bias when evaluating the confidence in study results.

In order to be comprehensive we also included reviews where both adults and children were included as well as studies where the exposure were domestic, as long as the same exposure is also known as an occupational exposure (e.g., paint and pesticide exposure). It can be argued that the circumstances can be different for domestic exposures and occupational exposures (e.g., exposure more hours/week, higher or lower exposure levels), but still we regarded the information useful. However, for three specific exposures (*Aspergillus, Cladosporium*, and *Penicllium species)* we downgraded the evidence from strong to moderate, as the conclusion on the most influential high quality review was based on susceptible individuals, and mainly domestic exposures among both children and adults. [22] In each systematic review, the original studies could include epidemiological

studies and/or clinical studies. A large proportion of the included studies were case studies, which in general is regarded as low evidence. But particular for asthma case studies with good quality specific inhalation challenges can be regarded as an experiment without significant confounder issues and with a high quality of both exposure and outcome data.

Discussion of results

Our overview clarifies the level of evidence and uncovers gaps in systematic knowledge of the relation between potential occupational sensitizing exposures and asthma. The overlap between this overview and the comprehensive systematic review by Baur et. al. (2014)[11] is substantial and is not surprising. Of note we found strong evidence of a relation between asthma and the main group of wood dust, and moderate evidence for main groups of mites and fish, which was not evaluated in Baur et al. (2014).[11] We found moderate evidence for 55 subgroups/specific exposures compared to 36 exposures documented by Baur. This is mainly due to new studies conducted after 2011 when Baur performed his literature search.[11] We did not find clear evidence of relations with asthma for many animals and specific enzymes regarded well known causes of asthma (for example mice and proteolytic enzymes). An obvious reason could be that researchers have not prioritizing performing systematic reviews on accepted risk factors.

We aimed to assess the evidence for potential occupational sensitizing exposures and asthma, and therefore we excluded reviews on exposures known to be irritants without any suspicion of a specific immunological mechanism, e.g., chlorine and ammonia. On the other hand, we included main and subgroup/specific exposures in order to be as comprehensive as possible at the expense of also including non-sensitizing exposures in our overview, so even though the purpose was to study potential occupational sensitizing exposures the overview to some extend also deals with irritants

without any specific mechanism of action. However, we did include exposures with partly nonspecific and irritative mechanisms, for example wood dust, isocyanates and cleaning agents, and we expect that some of the identified relations are based on non-specific mechanisms. By applying a structure with broad main groups as well as subgroups/specific exposure we aimed to be both comprehensive as well as transparent in our evaluations.

Perspectives

Identification of potential occupational sensitizing exposures in this and earlier reviews might help primary care physicians and occupational physicians in diagnosis and management of workers suffering from asthma and to prevent asthma in occupational settings. In future studies it is important to focus on exposure levels and exposure-response relations in order to perform specific and efficient prevention at the workplaces. Currently, specific occupational exposure limits are not available for sensitizing exposures, but for some exposures (e.g., specific enzymes),[30] data are available for setting health recommendations based occupational exposure limits. It is important to get access to similar knowledge for other exposures.

Conclusion

This overview summaries the current level of evidence of the relation between potential occupational sensitizing exposures and asthma. We found strong evidence of a relation for main groups of wood dust, and moderate evidence for mites and fish. For subgroups/specific exposures, strong evidence was found for exposure to various laboratory animals, and moderate evidence was found for 55 potential sensitizing exposures.

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Contributors

AD drafted the paper in close collaboration with VS. The study methodology and results were discussed among all authors. All authors have reviewed the paper for important intellectual content, approved the final version of the manuscript, and take responsibility for the integrity of the work as a whole.

Competing interest

None

Table 1. Characteristics of 22 systematic reviews of occupational exposures and asthma included in the systematic overview

Author	Searched electronic databases (date)	No. of included studies	Study designs included	Population	Exposures of interest	Outcome of interest	Comparators	Quality assessment of included studies	Assessment of evidence
Baur, 2013[31]	MEDLINE/PubMed (before August 2011)	865	NS	Working population	Occupational exposures	Self-reported, clinically assessed asthma	Within person or between group comparison	Modified SIGN	Modified RCGP
Baur, 2014[11]	MEDLINE/PubMed (before August 2011)	865	Case-control, case-reports, case-series, cohort and cross-sectional studies, follow-up of cases, systematic reviews	Working population	Occupational exposures	Self-reported, clinically assessed asthma	Within person or between group comparison	Modified SIGN	Modified RCGP
Canova, 2013[29]	PubMed (before May 2011)	20	Case-control, cohort, cross-sectional, experimental studies	General population (adults and children) (n=51 239)	Domestic paint	Self-reported, clinically assessed asthma	Between group comparison	No formal tool	Qualitative assessment
Cartier, 2015[15]	Medline (2012-June 2014)	10	Case-reports	Working population with asthma (n=18)	Occupational exposures	Clinically assessed asthma	Within person comparison	No formal tool	Qualitative assessment
Doust, 2014[32]	CINAHL, Cochrane Database of Systematic reviews, Embase, Google Scholar, Medline, PubMed, Scopus (1990-October 2010)	17(23)*	Case-control, cohort, cross-sectional studies, systematic review	Primary agricultural workers and children	Occupational and non-occupational pesticides	Clinically assessed asthma	Between group comparison	SIGN, summary grade (++, +, -)	Qualitative assessment
Folletti, 2014[25]	PubMed (1976-June 2012)	24	Case-control, cross-sectional, cohort studies	Cleaners in public or private buildings (n=71 163)	Cleaning products	Self-reported, clinically assessed asthma	Between group comparison	STROBE	Qualitative assessment
Jaakkola, 2006[26]	Medline (2003-November 2005)	12	Case-reports, case-control, cross-sectional studies	Domestic and industrial cleaners	Cleaning products	Self-reported, clinically assessed asthma	Within person or between group comparison	No formal tool	Qualitative assessment
Jaakkola, 2008[27]	Medline (1950-May 2007)	41	Case-reports, case-studies, case-control, cohort, cross-sectional, laboratory studies	Workers e.g., industry workers, children, and animals	Phthalate from PVC	Self-reported, clinically assessed asthma	Within person or between group comparison	No formal tool	Qualitative assessment including meta-analysis

ASSIA; Applied Social Sciences Index and Abstracts, DIRERAF; Development of Public Health Indicators for Reporting Environmental/Occupational Risk Related to Agriculture and Fishery, LILACS; Latin America and Caribbean, MERGE; Methods for Evaluating Research Guidance and Evidence, NIOSHTIC; National Institute of Occupational Safety and health, No; Number, NS; Not specified; RCGP; Royal College of General Practitioners, SIGN; Scottish Intercollegiate Guidelines Network. * Number in parenthesis is the total number of studies included in the review.

Table 1 cont. Characteristics of 22 systematic reviews of occupational sensitizing exposures and asthma included in the systematic overview

Author	Searched electronic databases (date)	No. of included studies	Study designs included	Population	Exposures of interest	Outcome of interest	Comparators	Quality assessment of included studies	Assessment of evidence
Jacobsen, 2010[19]	Medline (1969-June 2009)	17(25)*	Cohort, cross-sectional studies	Wood industry workers e.g., sawmill workers	Fresh wood and mixed wood dust	Self-reported, clinically assessed asthma	Between group comparison	No formal tool	Qualitative assessment
Jacobsen, 2010[17]	Medline (1969-June 2009)	16(37)*	Case-control, cohort, cross-sectional studies	Wood industry workers e.g., furniture workers	Dry wood dust	Self-reported, clinically assessed asthma	Between group comparison	No formal tool	Qualitative assessment
Jurewicz, 2007[24]	EBSCO, DIRERAF, MEDLINE, PubMed (1996-2006)	16	Cross-sectional studies	Greenhouse workers (n=32 822)	Bacterial and fungal biopesticides, endotoxin, fungi, mites	NS	Between group comparison	No formal tool	Qualitative assessment
Kolstad, 2002[23]	MEDLINE (1968-June 2000), NIOSHTIC (1977-June 2000)	14(59)*	Case-control, cohort, cross-sectional studies	Non-industrial workers e.g., day care and office workers, sample from populations (n=25 560)	Moulds in non-industrial indoor environments or dwellings	Self-reported, clinically assessed asthma	Between group comparison	Six quality parameters and total sum	Weighted average OR
Lai, 2013[16]	PubMed (2010-unknown) and included highly cited or important studies before 2010	8	Cohort studies	Textile/clothing industry workers	Textile dust	Clinically assessed asthma	Between group comparison	No formal tool	Qualitative assessment
Mamane, 2015[33]	MEDLINE/PubMed (before December 2013)	13(41)*	Case-control, cohort, cross-sectional studies	Agricultural and industry workers	Pesticides	Self-reported, clinically assessed asthma	Between group comparison	No formal tool	Qualitative assessment
Pérez-Ríos, 2010[20]	Embase (1980-2008), LILACS, ISI proceedings database (1990-2008), MEDLINE (1966-August 2008)	19	Case-control, cohort, mortality studies	General populations, woodworkers (n=18 040)	Wood dust	Self-reported, clinically assessed asthma	Between group comparison	5 point scale based on Newcastle-Ottawa scale	Meta-analysis
Reynolds, 2013[34]	Agricola, Ebesco, Google Scholar, Proquest, Scient Direct, PubMed, Web of Science (January 2002-September 2012)	7(30)*	Case-control, cohort, cross-sectional studies	Dairy workers, farmers (n=18 784)	Organic dust (dairy)	Self-reported, clinically assessed asthma, asthma symptoms	Between group comparison	No formal tool	Qualitative assessment

ASSIA; Applied Social Sciences Index and Abstracts, DIRERAF; Development of Public Health Indicators for Reporting Environmental/Occupational Risk Related to Agriculture and Fishery, LILACS; Latin America and Caribbean, MERGE; Methods for Evaluating Research Guidance and Evidence, NIOSHTIC; National Institute of Occupational Safety and health, No; Number, NS; Not specified; RCGP; Royal College of General Practitioners, SIGN; Scottish Intercollegiate Guidelines Network. * Number in parenthesis is the total number of studies included in the review.

Table 1 cont. Characteristics of 22 systematic reviews of occupational sensitizing exposures and asthma included in the systematic overview

Author	Searched electronic databases (date)	No. of included studies	Study designs included	Population	Exposures of interest	Outcome of interest	Comparators	Quality assessment of included studies	Assessment of evidence
Schlünssen, 1998[18]	Exerpta Medica, MEDLINE, NIOSHTIC (NS)	8(15)*	Cohort, cross-sectional studies	Industrial wood workers	Industrial wood dust (dry, not Red Cedar)	Self-reported, clinically assessed asthma	Between group comparison	No formal tool	Qualitative assessment
Sharpe, 2015[22]	AMED, ASSIA, British Nursing Index, Cochrane Library, Embase, Environment Complete, GreenFile Medline, Scopus, Web of Science (1990-April 2013)	17	Case-control, cohort, cross-sectional studies	Children and adults (n=7269)	Indoor home environment fungi	Self-reported, clinically assessed asthma	Between group comparison	Newcastle-Ottawa Scale (16 items)	Meta-analysis
Siracusa, 2013[28]	PubMed (1976-September 2012)	24	Case-control, case-reports, cohort, cross-sectional, panel studies	Indoor cleaning workers and cleaners in industrial settings, public or private buildings (n=320.455)	Cleaning products	Self-reported, clinically assessed asthma	Within person or between group comparison	No formal tool	Qualitative assessment
Wiggans, 2016[21]	Embase, HSE e-library, OSHUPDATE, ProQuest, PubMed, Web of Science (1970-December 2014)	8(55)*	Case-control, cohort studies, systematic review	Wood workers in wood processing and furniture manufacturing	Wood dust	Self-reported, clinically assessed asthma	Between group comparison	SIGN, MERGE	Meta-analysis
Wunschel, 2016[35]	PubMed (1999-NS)	14	Cohort, cross-sectional studies	Farming, agriculture workers	Organic dust, pesticides	NS	Between group comparison	No formal tool	Qualitative assessment
Zock, 2010[8]	MEDLINE (2006-2009)	18	Cohort, cross-sectional studies, review	Cleaners, adults (n=792 061)	Cleaning products	NS	Between group comparison	No formal tool	Qualitative assessment

ASSIA; Applied Social Sciences Index and Abstracts, DIRERAF; Development of Public Health Indicators for Reporting Environmental/Occupational Risk Related to Agriculture and Fishery, LILACS; Latin America and Caribbean, MERGE; Methods for Evaluating Research Guidance and Evidence, NIOSHTIC; National Institute of Occupational Safety and health, No; Number, NS; Not specified; RCGP; Royal College of General Practitioners, SIGN; Scottish Intercollegiate Guidelines Network. * Number in parenthesis is the total number of studies included in the review.

Table 2. AMSTAR 2 classification of 22 systematic reviews of occupational sensitizing exposures and asthma included in the systematic overview

Author	PICO	Protocol	Study desig explained	Compre-hensive literature search	Study selection duplicate	Data extractio duplicate	List of excluded studies	Description o included studi	RoB	Source of funding described	Meta-analysis performed	RoB in meta-analysis	Account RoB	f Hetero-genei described	Publication bi investi-gated	Conflict of interest stat	Overall confidence
Baur, 2013[31]	No	No	Yes	No	No	No	No	No	Partial yes	No	No meta-analysis conducted	No meta-analysis conducted	Yes	Low	No meta-analysis conducted	Yes	Moderate
Baur, 2014[11]	Yes	No	Yes	No	No	No	No	Partial yes	Partial yes	No	No meta-analysis conducted	No meta-analysis conducted	Yes	Yes	No meta-analysis conducted	Yes	Moderate
Canova, 2013[29]	Yes	No	No	No	No	No	No	Partial yes	No	No	No meta-analysis conducted	No meta-analysis conducted	No	No	No meta-analysis conducted	Yes	Low
Cartier, 2015[15]	Yes	No	Yes	No	No	No	No	No	No	No	No meta-analysis conducted	No meta-analysis conducted	No	No	No meta-analysis conducted	Yes	Low
Doust, 2014[32]	Yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Partial yes	No	No meta-analysis conducted	No meta-analysis conducted	Yes	Yes	No meta-analysis conducted	Partial yes	High
Folletti, 2014[25]	Yes	No	No	No	No	No	No	Partial yes	Partial yes	Yes	No meta-analysis conducted	No meta-analysis conducted	No	No	No meta-analysis conducted	Yes	Moderate
Jaakkola, 2006[26]	Yes	No	Yes	No	No	No	No	Partial yes	No	No	No meta-analysis conducted	No meta-analysis conducted	No	No	No meta-analysis conducted	No	Low
Jaakkola, 2008[27]	Yes	No	Yes	No	Yes	No	No	Partial yes	No	No	Yes	No	No	Yes	No	Yes	Low
Jacobsen, 2010[19]	Yes	No	No	No	No	No	No	Partial yes	Partial yes	No	No meta-analysis conducted	No meta-analysis conducted	No	Yes	No	No	Low
Jacobsen, 2010[17]	Yes	No	Yes	No	No	No	No	Partial yes	No	No	No meta-analysis conducted	No meta-analysis conducted	Yes	No	No meta-analysis conducted	Yes	Low
Jurewicz, 2007[24]	Yes	No	Yes	Partial yes	No	No	No	Partial yes	No	No	No meta-analysis conducted	No meta-analysis conducted	No	No	No meta-analysis conducted	Yes	Low

PICO; Population, Intervention, Comparison and Outcome, RoB; Risk of bias

Table 2 cont. AMSTAR 2 classification of 22 systematic reviews of occupational sensitizing exposures and asthma included in the systematic overview

Author	PICO	Protocol	Study designs explained	Compre-hensive literature search	Study selection duplicate	Data extractio duplicate	List of excluded studies	Description of included studies	RoB	Source of funding described	Meta-analysis performed	RoB in meta-analysis	Account for RoB	Hetero-geneity described	Publication bias investi-gated	Conflict of interest stated	Overall confidence
Kolstad, 2002[23]	Yes	No	Yes	No	No	No	No	Partial yes	Yes	No	No meta-analysis conducted	No meta-analysis conducted	Yes	Yes	No meta-analysis conducted	No	Moderate
Lai, 2013[16]	No	No	No	No	No	No	No	No	No	No	No meta-analysis conducted	No meta-analysis conducted	No	No	No meta-analysis conducted	Yes	Low
Mamane, 2015[33]	Yes	No	Yes	No	No	No	No	No	No	No	No meta-analysis conducted	No meta-analysis conducted	No	No	No meta-analysis conducted	Yes	Low
Pérez-Ríos, 2010[20]	Yes	Yes	Yes	Partial yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Reynolds, 2013[34]	Yes	No	No	No	No	No	No	Partial yes	No	No	No meta-analysis conducted	No meta-analysis conducted	No	No	No meta-analysis conducted	No	Low
Schlünssen, 1998[18]	No	No	No	No	No	No	No	No	No	No	No meta-analysis conducted	No meta-analysis conducted	Yes	No	No meta-analysis conducted	No	Low
Sharpe, 2015[22]	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Partial yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	High
Siracusa, 2013[28]	Yes	No	Yes	No	No	No	No	Partial yes	No	No	No meta-analysis conducted	No meta-analysis conducted	No	No	No meta-analysis conducted	Yes	Low
Wiggans, 2016[21]	Yes	No	Yes	Partial yes	Yes	No	No	Partial yes	Yes	Low	No meta-analysis conducted	No meta-analysis conducted	Yes	Yes	No meta-analysis conducted	Yes	Moderate
Wunschel, 2016[35]	Yes	No	No	No	No	No	No	No	No	No	No meta-analysis conducted	No meta-analysis conducted	No	No	No meta-analysis conducted	Yes	Low
Zock, 2010[8]	Yes	Low	No	No	No	No	No	Partial yes	No	No	No meta-analysis conducted	No meta-analysis conducted	No	No	No meta-analysis conducted	Yes	Low

PICO; Population, Intervention, Comparison and Outcome, RoB; Risk of bias

Table 3. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
ANIMALS (arachnids)							
Crustaceans							**Limited or contradictory evidence**
Lobster	Baur, 2014[11]	2	2	Clinical	No evidence	Moderate	
Prawn, Norway Lobsters	Baur, 2014[11]	2	22	Both	Moderate evidence	Moderate	(moderate)
Shrimp	Baur, 2014[11]	5	5	Both	Limited or contradictory evidence	Moderate	
Snow crab	Baur, 2014[11]	2	30	Both	Moderate evidence	Moderate	(moderate)
Insects							**No evidence**
Australia sheep blowfly	Baur, 2014[11]	2	1	Clinical	No evidence	Moderate	
Bee moth larvae	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Caddis fly	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Champignon flies	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Cockroach	Baur, 2014[11]	3	1	Clinical	No evidence	Moderate	
Common housefly	Baur, 2014[11]	2	1	Clinical	No evidence	Moderate	
Confused flour beetle	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Cricket	Baur, 2014[11]	3	4	Clinical	No evidence	Moderate	
Dermestidae spp. beetle	Baur, 2014[11]	2	2	Clinical	No evidence	Moderate	
Flour moth	Baur, 2014[11]	2	8	Both	Limited or contradictory evidence	Moderate	
Fruit fly	Baur, 2014[11]	1	3	Clinical	No evidence	Moderate	
Grain weevil	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Grasshopper	Baur, 2014[11]	1	4	Clinical	No evidence	Moderate	
Ground bugs	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Gypsy moth caterpillar	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Herring worm	Baur, 2014[11]	2	3	Clinical	No evidence	Moderate	
Honeybee	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Lentil pest	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Lesser mealworm	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Live fish bait	Baur, 2014[11]	3	16	Both	Limited or contradictory evidence	Moderate	
Locust	Baur, 2014[11]	3	19	Both	Moderate evidence	Moderate	(moderate)
Mealworm	Baur, 2014[11]	4	5	Clinical	Very limited or contradictory evidence	Moderate	
Mexican bean weevil	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Mosquito larvae	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Non-biting midges	Baur, 2014[11]	1	34	Both	Limited or contradictory evidence	Moderate	
Screwworm fly	Baur, 2014[11]	1	10	Both	Limited or contradictory evidence	Moderate	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Animals (arachnids)							
Insects (continued)							No evidence
Sewer fly	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Silkworm	Baur, 2014[11]	3	35	Both	Moderate evidence	Moderate	(moderate)
Tubifex tubifex	Cartier, 2015[15]	1	1	Clinical	Listed as causing asthma	Low	
Water-flea	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Various insects	Baur, 2014[11]	2	34	Clinical	No evidence	Moderate	
Mites							**Moderate evidence**
House dust mites	Baur, 2014[11]	3	14	Both	Limited or contradictory evidence	Moderate	
Poultry mites	Baur, 2014[11]	1	12	Both	Very limited or contradictory evidence	Moderate	
Predatory mites	Baur, 2014[11]	4	35	Both	Moderate evidence	Moderate	
Spider mites	Baur, 2014[11]	17	174	Both	Moderate evidence	Moderate	
Storage mites	Baur, 2014[11]	20	130	Both	Moderate evidence	Moderate	
Tyrophagus putrescentiae (dust mites)	Cartier, 2015[15]	1	1	Clinical	Listed as causing asthma	Low	
Molluscs							**No evidence**
Clam	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Cuttle-fish	Baur, 2014[11]	2	1	Clinical	No evidence	Moderate	
Green-lipped mussel	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Octopus	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Scallop	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Squid	Cartier, 2015[15]	1	1	Clinical	Listed as causing asthma	Low	
Other arachnida							**Limited or contradictory evidence**
Marine sponge	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Red soft corals	Baur, 2014[11]	1	9	Both	Limited or contradictory evidence	Moderate	
Animals (spinal cords)							
Birds							**Limited or contradictory evidence**
Budgerigar	Baur, 2014[11]	2	5	Both	Limited or contradictory evidence	Moderate	
Canary	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Various birds	Baur, 2014[11]	5	17	Both	Limited or contradictory evidence	Moderate	
Poultry	Baur, 2014[11]	3	18	Both	Limited or contradictory evidence	Moderate	
Fish							**Moderate evidence**
Atlantic Salmon, seafood, fishmeal, trout, turbot	Baur, 201411	7	28	Both	Moderate evidence	Moderate	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Mammals							**No evidence**
Black bat	Baur, 2014[11]	3	9	Clinical	Very limited or contradictory evidence	Moderate	
Cow	Baur, 2014[11]	6	84	Both	Moderate evidence	Moderate	(moderate)
Deer	Baur, 2014[11]	3	1	Both	No evidence	Moderate	
Elk	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Gerbil	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Guinea pig	Baur, 2014[11]	1	3	Clinical	No evidence	Moderate	
Horse	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Mink	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Monkey	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Mouse	Baur, 2014[11]	3	8	Both	Limited or contradictory evidence	Moderate	
Pig farming	Baur, 2014[11]	6	4	Clinical	No evidence	Moderate	
Reindeer	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Rat	Baur, 2014[11]	9	89	Both	Moderate evidence	Moderate	(moderate)
Sheep	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Animal products							**No evidence**
Beef, raw	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Bovine serum albumin	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Clam's liver	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Endocrine glands	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Honey	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Ivory	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Shark cartilage	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Milk proteins	Baur, 2014[11]	5	4	Clinical	No evidence	Moderate	
Egg proteins	Baur, 2014[11]	10	36	Both	Moderate evidence	Moderate	(moderate)
Amphibians							**No evidence**
Bull frog	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
PLANTS (excluding wood dust)							**No evidence**
Family Amaranthaceae							
Brazil ginseng root	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Apiacea							
Bishop's weed	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Plants (excluding wood dust), continued							**No evidence**
Carrot	Baur, 2014[11]	2	3	Clinical	No evidence	Moderate	
Coriander	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Fennel seed	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Araceae							
Banha	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Canari palm pollen	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Spathe flower	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Araliaceae							
Umbrella tree	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Madagascar jasmine	Baur, 2014[11]	1	4	Both	Limited or contradictory evidence	Moderate	
Family Bombacaceae							
Kapok	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Family Brassicaceae							
Arabidopsis thaliana	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Cabbage	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Cauliflower	Baur, 2014[11]	2	1	Clinical	No evidence	Moderate	
Oilseed rape flour	Baur, 2014[11]	2	3	Clinical	No evidence	Moderate	
White wall rocket pollen	Baur, 2014[11]	2	1	Clinical	No evidence	Moderate	
White mustard	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Family Cactacea							
Carnation	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Carnation	Baur, 2014[11]	4	15	Both	Very limited or contradictory evidence	Moderate	
Family Cannabaceae							
Hops	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Caryophyllaceae							
Baby's breath	Baur, 2014[11]	4	3	Clinical	No evidence	Moderate	
Family Chenopodiaceae							
Swiss chard	Baur, 2014[11]	2	2	Clinical	No evidence	Moderate	
Family Compositae = Asteraceae							
Artichoke, globe	Baur, 2014[11]	2	3	Clinical	No evidence	Moderate	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Plants (excluding wood dust)							**No evidence**
Camomile	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Chicory	Baur, 2014[11]	4	4	Clinical	No evidence	Moderate	
Chrysanthemum	Baur, 2014[11]	2	9	Both	Limited or contradictory evidence	Moderate	
Flowers	Baur, 2014[11]	2	6	Both	Limited or contradictory evidence	Moderate	
Lettuce	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Marigold flour	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Milk thistle	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Safflower	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Sunflower pollen	Baur, 2014[11]	3	3	Both	Limited or contradictory evidence	Moderate	
Sunflower seeds	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Yarrow	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Cucurbitaceae							
Courgette	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Euphorbiaceae							
Castor beans	Baur, 2014[11]	6	16	Both	Limited or contradictory evidence	Moderate	
Copperleaf	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Latex	Baur, 2014[11]	17	136	Both	Moderate evidence	Moderate	(moderate)
Plukenetia volubilis seeds	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Iridaceae							
Freesia	Baur, 2014[11]	2	1	Clinical	No evidence	Moderate	
Saffron pollen	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Lamiaceae							
Bells of Ireland, pollen	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Leguminosae							
Acacia	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Carob bean flour	Baur, 2014[11]	3	3	Clinical	No evidence	Moderate	
Chick pea	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Chickling vetch	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Green bean	Baur, 2014[11]	2	2	Clinical	No evidence	Moderate	
Guar gum	Baur, 2014[11]	2	6	Both	Limited or contradictory evidence	Moderate	
Gum Arabic	Baur, 2014[11]	2	11	Clinical	Very limited or contradictory evidence	Moderate	
Henna, black	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Lathyrus sativus flour	Baur, 2014[11]	2	2	Clinical	No evidence	Moderate	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Plants (excluding wood dust)							**No evidence**
Family Leguminosae (continued)							
Lentil	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Liquorice roots, licorice	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Mimosa	Baur, 2014[11]	1	4	Clinical	No evidence	Moderate	
Pea, perennial	Baur, 2014[11]	2	2	Clinical	No evidence	Moderate	
Senna	Baur, 2014[11]	4	6	Both	Limited or contradictory evidence	Moderate	
Vetch	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Liliaceae							
Amaryllis	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Asparagus	Baur, 2014[11]	3	10	Clinical	Very limited or contradictory evidence	Moderate	
Daffodil	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Easter Lily	Baur, 2014[11]	3	2	Clinical	No evidence	Moderate	
Garlic dust	Baur, 2014[11]	4	10	Clinical	Very limited or contradictory evidence	Moderate	
Hyacinth	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Onion	Baur, 2014[11]	2	2	Clinical	No evidence	Moderate	
Sarsaparilla root dust	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Tulip	Baur, 2014[11]	3	4	Clinical	No evidence	Moderate	
Sanyak	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Spice dust: Garlic	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Family Lythraceae							
Henna	Baur, 2014[11]	4	4	Clinical	No evidence	Moderate	
Family Moraceae							
Weeping fig	Baur, 2014[11]	4	10	Both	Limited or contradictory evidence	Moderate	
Family Myristicaceae							
Mace	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Myrsinaceae							
Cyclamen pollen	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Familiy Oleaceae							
Olive fruit	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Papaveraceae							
Poppy	Baur, 2014[11]	1	6	Both	Limited or contradictory evidence	Moderate	
Family Passifloraceae							
Passion flower leaves	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Plants (excluding wood dust)							**No evidence**
Family Pedaliaceae							
Sesame seeds	Baur, 2014[11]	2	1	Clinical	No evidence	Moderate	
Family Plantaginaceae							
Senna, Ispaghula husks	Baur, 2014[11]	1	4	Both	Limited or contradictory evidence	Moderate	
Psyllium	Baur, 2014[11]	11	31	Both	Moderate evidence	Moderate	(moderate)
Family Plumbaginaceae					-		
Statice	Baur, 2014[11]	2	1	Clinical	No evidence	Moderate	
Family Poaceae = Gramineae							
Esparto grass	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Grass juice	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Rice	Baur, 2014[11]	1	3	Clinical	No evidence	Moderate	
Family Rosacea							
Peach	Baur, 2014[11]	2	2	Clinical	No evidence	Moderate	
Raspberry	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Rose	Baur, 2014[11]	3	20	Both	Limited or contradictory evidence	Moderate	
Strawberry	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Rubiaceae							
Coffee: raw	Baur, 2014[11]	14	51	Both	Moderate evidence	Moderate	(moderate)
Ipecacuanha	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Family Solanaceae							
Eggplant pollen	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Paprika	Baur, 2014[11]	5	55	Both	Moderate evidence	Moderate	(moderate)
Potato	Baur, 2014[11]	2	2	Clinical	No evidence	Moderate	
Tobacco	Baur, 2014[11]	9	2	Both	Moderate evidence	Moderate	(moderate)
Family Sterculiaceae							
Cacao beans	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Theaceae							
Tea dust, various	Baur, 2014[11]	11	8	Both	Moderate evidence	Moderate	(moderate)
Other plant families							
Dried fruits and teas	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Flowers	Baur, 2014[11]	2	10	Both	Limited or contradictory evidence	Moderate	
Fibers, textile	Lai, 2013[16]	8	NS	Observational	Textile dust related obstructive lung disease has characteristic of both asthma and chronic obstructive lung disease	Low	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Plants (excluding wood dust)							**No evidence**
Other plant families (continued)							
Herbal tea (containing chaparral, red clover, mint etc.)	Baur, 2014[11]	1	-	Both	NS	Moderate	
Herbal tea	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Herbs, aromatic (thyme, rosemary, bay leaf, garlic)	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Lime flower	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Natural fibers, natural, not specified	Baur, 2014[11]	1	4	Clinical	No evidence	Moderate	
Orange tree aerollergen (cit s 3)	Cartier, 2015[15]	1	1	Clinical	Listed as causing asthma	Low	
Orange zest (flavedo)	Cartier, 2015[15]	1	1	Clinical	Listed as causing asthma	Low	
Pectin (carbohydrate of plant cells)	Baur, 2014[11]	2	2	Clinical	No evidence	Moderate	
Sisal	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Spices: Coriander (Coriandrum sativum) and other spices: mace (Myristica fragrans), ginger (Zingiber officinale), paprika (Capsicum tetragonum), curry.	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Tragacanth gum	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Voacanga africana seed dust	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Natural thickening products	Baur, 2014[11]	1	3	Clinical	No evidence	Moderate	
East African teak trees	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Exotic woods	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Maple	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Rimu	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Various woods	Baur, 2014[11]	4	11	Clinical	Very limited or contradictory evidence	Moderate	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Plants (wood dust)							**Strong evidence**
Other plant families (continued)							
Various (Abies, Chestnut, Douglas, Framire, Mansonia, Oak, Obeche, Walnut, White poplar)	Baur, 2014[11]	1	9	Both	Limited or contradictory evidence	Moderate	
Wood (Eucalypt, radiata pine, meranti, sugar pine, tasmanian oak, american oak, jarrah, tasmanian blackwood, wester red cedar)	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Wood dust (spruce)	Cartier, 2015[15]	1	1	Clinical	Listed as causing asthma	Low	
Wood dust (dry)	Jacobsen, 2010[17]	16	NS	Observational	The results support an relation between dry wood dust exposure and asthma	Low	
Wood dust (dry, not Red Cedar)	Schlünssen, 1998[18]130	9	NS	Observational	Despite methodological bias, there appears to be an relation between asthma and occupational exposure to wood dust processed from Danish wood species	Low	
Wood dust (fresh and mixed)	Jacobsen, 2010[19]	16	NS	Observational	The results supports an relation between fresh wood dust exposure and asthma	Low	
Wood dust (not specified)	Pérez-Ríos, 2010[20]	19	18 040	Observational	The results of the meta-analysis and their consistency across designs and settings provide evidence that exposure to wood dust may increase the risk of work-related asthma	High	
Wood dust (not specified)	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Wood dust (wood processing and furniture manufacturing industries)	Wiggans, 2016[21]	8	NS	Observational	This review found an increased risk of respiratory symptoms and asthma in people working in the wood processing and furniture manufacturing industries	Moderate	
Hardwood							
Family Bignoniaceae							
Ipe, Brazilian walnut	Baur, 2014[11]	2	2	Clinical	No evidence	Moderate	
Family Ebenaceae							
Ebony wood	Baur, 2014[11]	2	-	Clinical	No evidence	Moderate	
Family Fagaceae							
Beech	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Plants (wood dust)							**Strong evidence**
Family Fagaceae (continued)							
Cabreuva	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Oak	Baur, 2014[11]	3	-	Clinical	No evidence	Moderate	
Family Juglandaceae							
Central American walnut	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Family Lauraceae							
Imbuia (Phoebe porosa), Brazilian	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Walnut							
Family Meliaceae							
Mahogany	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Sapele wood	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Moraceae							
Antiaris	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Iroko	Baur, 2014[11]	3	5	Clinical	Very limited or contradictory evidence	Moderate	
Family Oleaceae							
Ash	Baur, 2014[11]	3	1	Clinical	No evidence	Moderate	
Family Rhamnaceae							
Cascara sagrada bark	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Rosacea							
Soapbark	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Rutaceae							
Pau marfin	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Family Sabotaceae							
Abiurana	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Makore, African cherry wood	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Tanganyika aningre	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Family Sterculiaceae							
African Maple	Baur, 2014[11]	7	16	Clinical	Very limited or contradictory evidence	Moderate	
Family Thymelaeceae							
Ramin	Baur, 2014[11]	3	2	Clinical	No evidence	Moderate	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Plants (wood dust)							**Strong evidence**
Softwood							
Family Cupressaceae							
California Redwood	Baur, 2014[11]	2	-	Clinical	No evidence	Moderate	
Eastern white cedar	Baur, 2014[11]	2	1	Both	Limited or contradictory evidence	Moderate	
Western red cedar	Baur, 2014[11]	14	323	Both	Moderate evidence	Moderate	(moderate)
Western red cedar	Cartier, 2015[15]	1	1	Clinical	Listed as causing asthma	Low	
Family Pinaceae							
Cedar of Lebanon	Baur, 2014[11]	2	1	Clinical	No evidence	Moderate	
Pine	Baur, 2014[11]	6	1	Both	Limited or contradictory evidence	Moderate	
Mould, fungi, yeast							**No evidence**
Edible mushrooms							
Boletus edulis	Baur, 2014[11]	3	8	Clinical	Very limited or contradictory evidence	Moderate	
Pleurotus cornucopiae	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Pleurotus ostreatus	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Moulds, other fungi							
Alternaria	Baur, 2014[11]	2	8	Both	Limited or contradictory evidence	Moderate	
Alernaria	Sharpe, 2015[22]	3	7269*	Observational	No association in longitudinal studies	High	
Aspergillus, various species	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Aspergillus niger	Baur, 2014[11]	2	12	Both	Moderate evidence	Moderate	(moderate)
Aspergillus fumigatus	Baur, 2014[11]	2	1	Clinical	No evidence	Moderate	
Aspergillus fumigatus	Cartier, 2015[15]	1	1	Clinical	Listed as causing asthma	Low	
Aspergillus	Sharpe, 2015[22]	5	7269*	Observational	Longitudinal studies assessing increased exposure to indoor fungi before the development of asthma symptoms suggest that Aspaergillus pose a respiratory health risk in susceptible populations	High	(moderate^{++})
Chrysonilia sitophila, common red bread mould	Baur, 2014[11]	3	3	Clinical	No evidence	Moderate	
Cladosporium	Sharpe, 2015[22]	6	7269*	Observational	Longitudinal studies assessing increased exposure to indoor fungi before the development of asthma symptoms suggest that Cladosporium pose a respiratory health risk in susceptible populations	High	(moderate^{++})

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Mould, fungi, yeast (continued)							**No evidence**
Dictyostelium discoideum, slime mould	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Moulds (non-industrial)	Kolstad, 2002[23]	14	25 560*	Observational	The studies provide no evidence that increasing levels of viable mould exposure in nonindustrial work environments or dwellings are related to an increased occurrence of asthma	Moderate	
Mucor	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Neurospora sp.	Baur, 2014[11]	2	2	Clinical	No evidence	Moderate	
Penicillium camemberti	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Penicllium	Sharpe, 2015[22]	5	7269*	Observational	Longitudinal studies assessing increased exposure to indoor fungi before the development of asthma symptoms suggest that Penicllium pose a respiratory health risk in susceptible populations	High	(moderate^{++})
Plasmopara viticola, pseudo mildew of Grapevine	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Rhizopus nigricans	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Scopulariopsis brevicaulis	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Sporobolomyces salmonicolor	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Mould fungi (Mucor Aspergillus and)	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Yeast							
Saccharomyces cerevisiae	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Microscopic organisms (Protoctistae)							
Chlorella (algae)	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	

++The evaluation was based on susceptible individuals, and mainly domestic exposures among both children and adults. So the a priori strong evidence was downgraded to moderate evidence

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Enzymes							**Limited or contradictory evidence**
a-amylase from Aspergillus oryzae	Baur, 2014[11]	11	29	Both	Moderate evidence	Moderate	(moderate)
a-amylase inhibitors of cereal origin	Baur, 2014[11]	1	3	Clinical	No evidence	Moderate	
Alfa-amylase termanyl	Cartier, 2015[15]	1	1	Clinical	Listed as causing asthma	Low	
Amylase from Bacillus licheniformis	Baur, 2014[11]	1	4	Clinical	No evidence	Moderate	
Aspergillus enzymes (a-amylase, cellulase)	Baur, 2014[11]	1	9	Clinical	Very limited or contradictory evidence	Moderate	
Aspergillus oryzae enzymes (amylase, protease)	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Beta-glucanase and phytase	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Bromelain of Ananas comosus	Baur, 2014[11]	4	13	Both	Limited or contradictory evidence	Moderate	
Cellulase, not specified	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Cellulase from Aspergillus niger	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Cellulase from Trichoderma reesei	Baur, 2014[11]	1	7	Observational	Very limited or contradictory evidence	Moderate	
Cellulase from Trichoderma viride	Baur, 2014[11]	1	2	Both	Limited or contradictory evidence	Moderate	
Cellulase from Trichoderma viridae, Fusarium moniliform	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Detergent enzymes	Baur, 2014[11]	5	53	Both	Moderate evidence	Moderate	(moderate)
Enzyme powder in cheese production, fungal and pancreatic	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Enzymes a-amylase and lysozyme	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Enzymes (Amylase, Cellulase, Protease)	Baur, 2014[11]	1	54	Both	Limited or contradictory evidence	Moderate	
Enzymes (α-amylase bacterial), α-amylase (fungal), cellulase, phytase, xylanase)	Baur, 2014[11]	1	1	Both	Limited or contradictory evidence	Moderate	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Enzymes (continued)							**Limited or contradictory evidence**
Enzymes (amylase, bromelain,chymotrypsin lipase, papain, trypsin)	Baur, 2014[11]	1	4	Clinical	No evidence	Moderate	
Flaviastase from Aspergillus niger	Baur, 2014[11]	1	3	Clinical	No evidence	Moderate	
Glucoamylase (amyloglucosidase) from Aspergillus niger	Baur, 2014[11]	1	4	Clinical	No evidence	Moderate	
Glucose oxidase from Aspergillus niger	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Lactase from Aspergillus	Baur, 2014[11]	1	9	Both	Limited or contradictory evidence	Moderate	
Lysozyme (lysozyme chloride)	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Microbial transglutaminase	Cartier, 2015[15]	1	1	Clinical	Listed as causing asthma	Low	
Pancreatin (porcine and bovine)	Baur, 2014[11]	4	19	Clinical	Very limited or contradictory evidence	Moderate	
Papain (Carica papaya)	Baur, 2014[11]	11	109	Both	Moderate evidence	Moderate	(moderate)
Pectinase from Aspergillus niger	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Pectinase from Aspergillus niger and glucanase from Trichoderma	Baur, 2014[11]	1	3	Clinical	No evidence	Moderate	
Pepsin (porcine)	Baur, 2014[11]	3	3	Clinical	No evidence	Moderate	
Peptidase from Serratia ssp.	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Phytase from Aspergillus niger	Baur, 2014[11]	2	12	Both	Moderate evidence	Moderate	(moderate)
Proteolytic enzymes derived from Bacillus species	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Savinase (subtilase family)	Cartier, 2015[15]	1	1	Clinical	Listed as causing asthma	Low	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Enzymes (continued)							**Limited or contradictory evidence**
Proteolytic enzymes: Alcalase	Baur, 2014[11]	1	6	Clinical	Very limited or contradictory evidence	Moderate	
Protease, Pronase E from Streptomyces	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Rennet not specified and of Endothica parasitica	Baur, 2014[11]	2	1	Clinical	No evidence	Moderate	
Trypsin (porcine), inactivated	Baur, 2014[11]	1	4	Both	Limited or contradictory evidence	Moderate	
Xylanase from Aspergillus niger	Baur, 2014[11]	2	3	Clinical	No evidence	Moderate	
Various enzymes	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Various enzymes from Bacillus subtilis (alcalase, protease, maxatase, maxapem, esperase, cellulase, a-amylase, lipase, subtilisin)	Baur, 2014[11]	13	327	Both	Moderate evidence	Moderate	(moderate)
Biocides and chemicals							
Drugs							**No evidence**
Aescin	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
α-methyldopa	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Aminophylline	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Amprolium hydrochloride	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Cephalosporin	Baur, 2014[11]	6	8	Both	Limited or contradictory evidence	Moderate	
Cimetidine	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Ciprofloxacin	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Hydralazine	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Isonicotinic acid hydrazide (INH)	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Lasamide (Intermediate of Furosemide)	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Mitoxantrone	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Opiates	Baur, 2014[11]	7	28	Both	Moderate evidence	Moderate	(moderate)
Penicillines	Baur, 2014[11]	9	4	Clinical	Limited or contradictory evidence	Moderate	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included persons	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Biocides and chemicals							
Drugs (continued)							**No evidence**
Phenylglycine acid chloride (side chain of Ampicillin, Cephalexin, cephaloglycin)	Baur, 2014[11]	1	4	Clinical	Limited or contradictory evidence	Moderate	
Potassium tetrachloroplatinate	Cartier, 2015[15]	1	1	Clinical	Listed as causing asthma	Low	
Salbutamol base	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Salbutamol inter-mediateglycyl compound powder	Baur, 2014[11]	1	-	Both	Not described	Moderate	
Spiramycin	Baur, 2014[11]	4	2	Clinical	No evidence	Moderate	
Tetracycline	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Thiamine	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Tylosin tartrate	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Polymyxin E (Colistin)	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Metals							**No evidence**
Aluminium	Baur, 2014[11]	2	1	Clinical	No evidence	Moderate	
Chromium	Baur, 2014[11]	2	5	Clinical	No evidence	Moderate	
Chromium and nickel	Baur, 2014[11]	4	13	Clinical	Very limited or contradictory evidence	Moderate	
Chromate	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Cobalt	Baur, 2014[11]	3	2	Clinical	No evidence	Moderate	
Cobalt and nickel	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Iron	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Manganese	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Nickel sulphate	Baur, 2014[11]	2	2	Clinical	No evidence	Moderate	
Platinum salts	Baur, 2014[11]	8	96	Both	Moderate evidence	Moderate	(moderate)
Palladium	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Vanadium	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Zinc	Baur, 2014[11]	2	1	Clinical	No evidence	Moderate	
Rhodium salts	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Dyes							Limited or contradictory evidence
Carmine	Baur, 2014[11]	8	11	Both	Moderate evidence	Moderate	(moderate)
Carmine red	Cartier, 2015[15]	1	1	Clinical	Listed as causing asthma	Low	
Indigotine	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Henna (black)	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Lanasol dyes	Baur, 2014[11]	1	4	Clinical	No evidence	Moderate	
Monascus ruber	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Reactive dyes	Baur, 2014[11]	5	28	Both	Moderate evidence	Moderate	(moderate)
Biocides							**No evidence**
4,4-Methylene-bismorpholine	Cartier, 2015[15]	1	1	Clinical	Listed as causing asthma	Low	
Chloramine T	Baur, 2014[11]	3	9	Clinical	Very limited or contradictory evidence	Moderate	
Glutaraldehyde	Baur, 2014[11]	4	1	Clinical	No evidence	Moderate	
Chlorhexidine	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Chlorhexidine	Cartier, 2015[15]	1	2	Both	Listed as causing asthma	Low	
Hexachlorophene	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Ortho-phthalaldehyde	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Peracetic acid, hydrogen peroxide	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Pesticides	Doust, 2014[32]	17	NS	Observational	Sufficient evidence to suggest that pesticides may be associated with greater prevalence of asthma especially in children (less convincing in adults)	High	
Pesticides (agriculture and industries)	Mamane, 2015[33]	13	170 313*	Observational	It is uncertain whether pesticides cause asthma or act as a trigger for asthma exacerbation, or both	Low	
Tetrachloroisophtha-lonitrile	Baur, 2014[11]	1	-	Both	No evidence	Moderate	
Captafol	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Tributyl tin oxide	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Fluazinam and chlorothalonil	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Isocyanates							Limited or contradictory evidence
Hexamethylene diisocyanate (HDI)	Baur, 2014[11]	1	3	Both	Limited or contradictory evidence	Moderate	
1,5-naphthalene diisocyanate (NDI)	Baur, 2014[11]	3	-	Clinical	No evidence	Moderate	
Methylene diphenyl-diisocyanate (MDI)	Baur, 2014[11]	7	10	Both	Moderate evidence	Moderate	(moderate)
Toluene diisocyanates	Baur, 2014[11]	4	9	Both	Moderate evidence	Moderate	(moderate)
Triglycidyl isocyanurate (TGIC)	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Various isocyanates	Baur, 2014[11]	6	22	Both	Moderate evidence	Moderate	(moderate)
Anhydrides							**Limited or contradictory** evidence
Tetrachlorophthalic anhydride	Baur, 2014[11]	2	7	Clinical	Very limited or contradictory evidence	Moderate	
Phthalic anhydride	Baur, 2014[11]	4	6	Both	Moderate evidence	Moderate	(moderate)
Phthalic anhydride and chlorendic anhydride	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Methyl tetrahydrophthalic anhydride (MTHPA)	Baur, 2014[11]	2	3	Both	Limited or contradictory evidence	Moderate	
Hexahydrophthalic anhydride	Baur, 2014[11]	2	5	Both	Limited or contradictory evidence	Moderate	
Maleic anhydride	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Trimellitic anhydride	Baur, 2014[11]	1	4	Both	Limited or contradictory evidence	Moderate	
Various anhydrides	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Amines							**No evidence**
Amino-ethyl ethanolamine	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Dimethyl ethanolamine	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Ethylenediamine	Baur, 2014[11]	2	2	Clinical	No evidence	Moderate	
Ethanolamine and Triethanolamine	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Diethanolamine	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Paraphenylenediamine	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Piperazine	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Amines (continued)							**No evidence**
Piperazine dihydrochloride	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Piperazine and n-methyl-piperazine	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Piperazine citrate	Baur, 2014[11]	1	1	Clinical	No evidence	Moderate	
Other chemicals compounds							**Limited or contradictory evidence**
Azodicarbonamide	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Acrylic resin	Cartier, 2015[15]	1	1	Clinical	Listed as causing asthma	Low	
Cleaning products i.e. cleaning sprays, bleach, mixing products	Folletti, 2014[25]	24	71163*	Observation	Level of exposure to cleaning products, cleaning sprays, bleach, mixing products has been identified as specific causes of asthma	Moderate	(moderate)
Cleaning products i.e., bleach, disinfectants including glutaraldehyde, formaldehylde	Jaakkola, 2006[26]	12	7247*	Both	Identification of chemicals such as bleach, and disinfectants including glutaraldehyde or formaldehylde, as specific causes of asthma	Low	(moderate)
Cleaning products i.e., cleaning sprays, bleach, disinfectants (e.g., chloamine-T, quaternary ammonium compounds, and ethanolamine), mixing products	Siracusa, 2013[28]	25	310 860*	Both	Cleaning sprays, bleach, disinfectants (e.g., chloamine-T, quaternary ammonium compounds, and ethanolamine), mixing products, and specific job tasks have been identified as specific causes of or exacerbation for asthma	Low	(moderate)
Cleaning products	Zock, 2010[8]	21	792 061*	Observational	Recent studies have strengthened the evidence of asthma in cleaning workers. Similar effects are seen in other settings in which cleaning products are used as healthcare professionals and homemakers. Both new-onset and work-exacerbated asthma due to cleaning products may play a role	Low	(moderate)

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Other chemicals compounds (continued)							**Limited or contradictory evidence**
Cyanoacrylate	Cartier, 2015[15]	1	1		Listed as causing asthma	Low	
Epoxy resin	Baur, 2014[11]	4	-	Clinical	No evidence	Moderate	
Formalin, formaldehyde	Baur, 2014[11]	6	1	Clinical	No evidence	Moderate	
Paints	Canova, 2013[29]	20	51239*	Observation	Inadequate evidence	Low	
Persulphate salts and henna	Baur, 2014[11]	1	2	Clinical	No evidence	Moderate	
Persulphate salts	Baur, 2014[11]	4	19	Both	Limited or contradictory evidence	Moderate	
Phthalates from PVC	Jaakkola, 2008[27]	41	NS	Both	Heated PCV fumes possibly contribute to development of asthma in adults	Low	
PVC powder	Cartier, 2015[15]	1	2	Clinical	Listed as causing asthma	Low	
Polyfunctional aziridine	Baur, 2014[11]	1	4	Both	Limited or contradictory evidence	Moderate	
Sensitizing exposures in specific occupations/worksites							**Limited or contradictory evidence**
Farming							
Farming: animals, cereal, hay and straw, storage mites	Baur, 2014[11]	1	30	Both	Moderate evidence	Moderate	(moderate)
Co-exposure to various laboratory animals	Baur, 2014[11]	19	140	Both	Strong evidence	Moderate	(moderate)
Organic dust (farming and argiculture)	Wunschel, 2016[35]	14	NS	Observational	Longer exposure to occupational farming is associated with decreased asthma risk. However, studies also suggest that agricultural work and multiple types of livestock are independent risk factors for developing asthma	Low	
Dairy workers							
Organic dust (dairy workers)	Reynolds, 2013[34]	7	18 784*	Observational	Dairy workers have an increased risk of asthma	Low	
Bakery							
Alkaline hydrolysis wheat gluten derivative	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Bakery (flour, amylase, storage mites)	Baur, 2014[11]	21	174	Both	Moderate evidence	Moderate	(moderate)
Barley (Hordeum vulgare)	Baur, 2014[11]	1	-	Clinical	No evidence		

Table 3 cont. Potential occupational sensitizing exposures and asthma reported in 22 systematic reviews

Allergens	Author	Number of included studies	Number of included cases*	Type of studies in the review (observational and/ or clinical studies)	Study conclusion	Review quality rating (AMSTAR 2)	Evidence of association (GRCP)
Bakery (continued)							
Buckwheat (Fagopyrum esculentumor schulentum)	Baur, 2014[11]	4	4	Clinical	No evidence	Moderate	
Rye flour (Secale cereale)	Baur, 2014[11]	2	7	Clinical	Very limited or contradictory evidence	Moderate	
Soybean processing (bakery, animal feeding, food processing)							
Soybean (hulls, flour, enzymes)	Baur, 2014[11]	11	25	Both	Moderate evidence	Moderate	(moderate)
Brewery							
Brewery	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Welding							
Stainless steel welding fumes	Baur, 2014[11]	1	-	Clinical	No evidence	Moderate	
Greenhouse workers				Both			
Dust, bacteria, allergens, fungi and gases	Jurewicz, 2007[24]	16	NS	Observational	Exposure to dust, bacteria, allergens, fungi and gases may cause or exacerbate asthma	Low	

OR; Odds ratio, * Total population

APPENDIX

Appendix 1: PECO for peer-reviewed systematic reviews

Population

Adult human population in or above working age

Exposure

Exposure definition: Primary exposures included occupational sensitizing exposures suspected to cause asthma. The sensitizing exposures included both high- and certain low-molecular-weight exposures, which were divided into the following groups;

- Animals (i.e., *arachnida*: crustaceans, insects, mites, molluscs, other arachnida, *spinal cords:* birds, fish, mammals amphibians, *animal products and others:* animals products)
- Plants (i.e., plants excluding wood dust and wood dust)
- Mould, fungi, yeast
- Enzymes
- Biocides and chemicals (i.e., drugs, metals, dyes, biocides, isocyanates, anhydrides, amines, and other chemical compounds)
- Occupation

Exposure assessment: We included studies with exposure information based on subjective (self-reports) or objective assessment (e.g., expert based, observations, technical measurements), and where exposure estimates were quantified ranging from dichotomous to continuous variables. Studies with more proxy measure of exposures such as job title or industry (no exposure quantification) was not included.

Comparison

We included studies in which a relation between occupational sensitizing exposures and asthma has been evaluated.

Outcome

Outcome definition: Outcome was defined as asthma. Asthma wss considered a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper-responsiveness, and an underlying inflammation. Outcome did not include pre-existing asthma aggravated by work (difficult to evaluate).

Outcome assessment: We included studies, where outcome was assessed as:

- Self-reported by workers, or
- Clinical diagnosis as reported by workers, or
- Clinical diagnosis by medical expert, or
- Objective measurements: spirometry (LFT, PET), immunology (as marker of effect), and provocation (lung) as the latter verification by experimental condition will be more specific.

Appendix 2: Full search string for literature search in MEDLINE/PudMed

((((((((((((((((((((((((((signs and symptoms, respiratory[MeSH Terms])) OR ((allergy and immunology[MeSH Terms]))) OR allergy[Text Word]) OR immunology[Text Word]) OR "respiratory function tests"[MeSH Terms]) OR respiratory function test*[Text Word]) OR pulmonary function test*[Text Word]) OR lung function test*[Text Word]) OR bronchial hyperreactivity[MeSH Terms]) OR bronchial hyperreactivit*[Text Word]) OR airway obstruction[MeSH Terms]) OR airway obstruction[Text Word]) OR respiratory hypersensitivity[MeSH Terms]) OR airway hyper responsiveness[Text Word]) OR respiratory hyper responsiveness[Text Word]) OR respiratory hypersensitivit*[Text Word]) OR lung diseases, obstructive[MeSH Terms]) OR obstructive lung disease*[Text Word]) OR obstructive pulmonary disease*[Text Word]) OR asthma[MeSH Terms]) OR asthma, occupational[MeSH Terms]) OR occupational asthma*[Text Word])) **AND** ((((((((((((workplace[MeSH Terms]) OR occupational exposure[MeSH Terms]) OR occupational diseases[MeSH Terms]) OR occupational exposure*[Text Word]) OR work related[Text Word]) OR workplace*[Text Word]) OR work environment[Text Word]) OR job site*[Text Word]) OR work location*[Text Word]) OR work site*[Text Word]) OR work place*[Text Word]) OR occupation[Text Word]) OR work[MeSH Terms])) **AND** ((((((((((((((((((allergens[MeSH Terms]) OR allergic[Text Word]) OR allergen*[Text Word]) OR antigen*[Text Word]) OR antigens[MeSH Terms]) OR hypersensitivit*[Text Word]) OR immediate[Text Word]) OR ige[Text Word]) OR immunoglobulin e[Text Word]) OR sensation[MeSH Terms]) OR hypersensitivity, immediate[MeSH Terms]) OR ((bites and stings[MeSH Terms]))) OR fungi[MeSH Terms]) OR dust[MeSH Terms]) OR feathers[MeSH Terms]) OR sensitization[Text Word]) OR sensitisation[Text Word]) OR asthmogen*[Text Word]) OR asthmagen*[Text Word])) **AND** ((((((((((((((((causality[MeSH Terms]) OR etiology[MeSH Terms]) OR risk factors[MeSH

Terms]) OR etiology[MeSH Subheading]) OR causation[Text Word]) OR causing[Text Word]) OR causalit*[Text Word]) OR etiolog*[Text Word]) OR epidemiolog*[Text Word]) OR reinforcing factor*[Text Word]) OR enabling factor*[Text Word]) OR predisposing factor*[Text Word]) OR odds ratio[MeSH Terms]) OR odds ratio*[Text Word]) OR risk[MeSH Terms]) OR incidence proportion rate*[Text Word]) OR incidence[MeSH Terms]) OR incidence rate*[Text Word])))
NOT ((animals[MeSH Terms]) NOT humans[MeSH Terms])))
AND ((danish[Language]) OR english[Language])
AND (review, meta-analysis)

Appendix 3: Study exclusion criteria

1) The following exclusion criteria were used at title screening:

- No indication of asthma or "unspecific lung disease" as *outcome* measure, or no outcome mentioned in the title, or
- No indication of occupational sensitizing exposures as *exposure*, or no exposure mentioned in the title, or
- No indication of a causal relationship between occupational sensitizing exposures and asthma-related outcomes
- Other reasons: Animal study, children/student study, not a review e.g., book, letter to editor, conference abstract, not English/Danish language

2) The following exclusion criteria were used at abstract screening:

- No indication of asthma or "unspecific lung diseases" as outcome measure, or
- No indication of occupational sensitizing exposures as exposure, or
- No indication of evaluation of the relation between asthma and occupational sensitizing exposures, or
- Other reasons: Animal study, children/student study, or, not a review e.g., book, letter to editor, conference abstract, abstract only, not a systematic review; abstract should indicate that the literature search was performed systematic, not English/Danish language

3) The following exclusion criteria were used at full paper reading:

- Study outcome does not fulfill outcome definition (i.e., outcome definition in PECO), or
- Study exposures does not fulfill exposure definition (i.e., exposure definition in PECO), or

- No indication of evaluation of the relation between asthma and occupational sensitizing exposures, or
- Other reasons: Animal study, children/student study, or, not a review e.g., book, letter to editor, conference abstract, abstract only, not a systematic review; abstract should indicate that the literature search was performed systematic, not English/Danish language

Appendix 4. Degree of evidence of the relation between main groups of occupational sensitizing exposures and asthma

Evidence level	Description
Strong evidence	• Generally consistent findings in ≥1 high quality-rated systematic review(s), or • Generally consistent findings in ≥2 moderate quality-rated systematic reviews
Moderate evidence	• Generally consistent findings in 1 moderate quality-rated systematic review, or • Generally consistent findings in ≥2 low quality-rated systematic reviews (e.g., 1 low and 1 moderate quality scored review)
Limited or contradictory evidence	• Generally consistent findings in 1 low quality-rated systematic review, or • Generally consistent findings in ≥2 very low quality-rated systematic reviews, or • Contradictory findings in ≥1 systematic review(s) with low to high quality rating
Very limited or contradictory evidence	• Generally consistent findings in 1 very low quality-rated systematic reviews, or • Contradictory findings in ≥1 systematic reviews with very low quality rating
No evidence	• Generally no evidence in ≥1 systematic review(s)

Appendix 5. Degree of evidence of the relation between subgroups/specific occupational sensitixzing exposures and asthma

Evidence level	Description
Strong evidence	• Association found in ≥1 high quality-rated systematic review(s), or • Generally consistent findings in ≥2 moderate quality-rated systematic reviews
Moderate evidence	• Association found in 1 moderate quality-rated systematic review, or • Generally consistent findings in ≥2 low quality-rated systematic reviews (e.g., 1 low and 1 moderate quality rated review)
Limited or contradictory evidence	• Association found in 1 low quality-rated systematic review, or • Generally consistent findings in ≥2 very low quality-rated systematic reviews, or • Contradictory findings in ≥1 systematic review(s) with low to high quality rating
Very limited or contradictory evidence	• Association found in 1 very low quality-rated systematic reviews, or • Contradictory findings in ≥2 systematic reviews with very low quality rating
No evidence	• Generally no evidence in ≥1 systematic review(s)

Appendix 6: List of excluded studies

Excluded studies	Reason for exclusion
Bousquet J, Flahault A, Vandenplas O, Ameille J, Duron, JJ, Pecquet, C, Chevrie K, Annesi-Maesano I. Natural rubber latex allergy among health care workers: A systematic review of the evidence. Journal of Allergy and Clinical Immunology 2006;118(2):447-454.	Study outcome does not fulfill outcome definition (i.e. PECO)
Diller WF. Frequency and trends of occupational asthma due to toluene diisocyanate: a critical review. Applied occupational and environmental hygiene Dec 2002;17(12):872-7.	Study outcome does not fulfill outcome definition (i.e. PECO)
Dumas, O.; Kauffmann, F.; Le Moual, N. Asthma and exposure to cleaning products. Archives Des Maladies Professionnelles Et De L Environnement 2013;74(2):117-129.	Other reason (e.g. not a systematic review)
Eduard, Wijnand. Fungal spores: A critical review of the toxicological and epidemiological evidence as a basis for occupational exposure limit setting. Critical reviews in toxicology 2009;39(10):799-864.	Other reason (e.g. not a systematic review)
Folletti I.; Paolocci G.; Murgia N.; Abraha I.; Dell'Omo M.; Gambelunghe A.; Giuliani A.; Muzi G. Indoor occupational risk-factor in nonindustrial settings and work-related asthma. A systematic review. Allergy: European Journal of Allergy and Clinical Immunology / 2015;70.	Other reason (e.g. not a systematic review)
Folletti I.; Siracusa A.; Paolocci G. Update on asthma and cleaning agents. Current Opinion in Allergy and Clinical Immunology / 2017;17(2):90-95.	Other reason (e.g. not a systematic review)
Garabrant DH.; Schweitzer S. Epidemiology of latex sensitization and allergies in health care workers. The Journal of allergy and clinical immunology Aug 2002;110(2 Suppl):S82-95.	Other reason (e.g. not a systematic review)
Goldsmith D.F.; Shy C.M. Respiratory health effects from occupational exposure to wood dusts Scandinavian Journal of Work, Environment and Health / 1988;14(1):1-15.	Other reason (e.g. not a systematic review)
Gordon, S.; Preece, R. Prevention of laboratory animal allergy. Occupational Medicine-Oxford 2003;53(6):371-377.	Study outcome does not fulfill outcome definition (i.e. PECO)
Jeebhay MF.; Ngajilo D.; le Moual N. Risk factors for nonwork-related adult-onset asthma and occupational asthma: a comparative review. Current opinion in allergy and clinical immunology Apr 2014;14(2):84-94.	No indication of evaluation of association between allergens and asthma

Jeebhay, Mohamed F.; Cartier, Andre. Seafood workers and respiratory disease: an update. Current Opinion in Allergy and Clinical Immunology 2010;10(2):104-113.	Study outcome does not fulfill outcome definition (i.e. PECO)
King ME.; Mannino DM.; Holguin F. Risk factors for asthma incidence. A review of recent prospective evidence.Panminerva medica Jun 2004;46(2):97-110	Other reason (e.g. not a systematic review)
Kongerud J.; Søyseth V. Respiratory disorders in aluminum smelter workers. Journal of occupational and environmental medicine May 2014;56(5 Suppl):S60-70 2014 May.	Study outcome does not fulfill outcome definition (i.e. PECO)
Korsgaard J. House-dust mites and asthma. A review on house-dust mites as a domestic risk factor for mite asthma. Allergy 1998;53(48 Suppl):77-83.	Other reason (e.g. not a systematic review)
LaMontagne AD.; Radi S.; Elder DS.; Abramson MJ.; Sim M. Primary prevention of latex related sensitisation and occupational asthma: a systematic review. Occupational and environmental medicine May 2006;63(5):359-64.	Study outcome does not fulfill outcome definition (i.e. PECO)
Liu Q.; Wisnewski AV. Recent developments in diisocyanate asthma. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology May 2003;90(5 Suppl 2):35-41.	Other reason (e.g. not a systematic review)
May, Sara; Romberger, Debra J.; Poole, Jill A. Respiratory Health Effects of Large Animal Farming Environments. Journal of Toxicology and Environmental Health-Part B-Critical Reviews 2012;15(8):524-541.	Other reason (e.g. not a systematic review)
Mendy A.; Gasana J.; Forno E.; Vieira ER.; Dowdye C. Work-related respiratory symptoms and lung function among solderers in the electronics industry: a meta-analysis. Environmental health and preventive medicine May 2012;17(3):183-90.	Study outcome does not fulfill outcome definition (i.e. PECO)
Mirer, Franklin E. New Evidence on the Health Hazards and Control of Metalworking Fluids Since Completion of the OSHA Advisory Committee Report. American Journal of Industrial Medicine 2010;53(8):792-801.	Study outcome does not fulfill outcome definition (i.e. PECO)
Ngajilo D.; Jeebhay M.F. Risk factors for general adult-onset and occupational asthma? A review of the literature: Allergies in the workplace. Current Allergy and Clinical Immunology / 2013;26(2):82-88.	Study exposure does not fulfill exposure definition (i.e. PECO)

Ott MG. Occupational asthma, lung function decrement, and toluene diisocyanate (TDI) exposure: a critical review of exposure-response relationships. Applied occupational and environmental hygiene Dec 2002;17(12):891-901.	No indication of evaluation of association between allergens and asthma
Pala G.; Moscato G. Allergy to ortho-phthalaldehyde in the healthcare setting: advice for clinicians. Expert review of clinical immunology Mar 2013;9(3):227-34.	Other reason (e.g. not a systematic review)
Quirce, Santiago; Sastre, Joaquin. New causes of occupational asthma. Current Opinion in Allergy and Clinical Immunology 2011;11(2):80-85.	Other reason (e.g. not a systematic review)
Samadi, Sadegh; Wouters, Inge M.; Heederik, Dick J. J. A review of bio-aerosol exposures and associated health effects in veterinary practice. Annals of Agricultural and Environmental Medicine 2013;20(2):206-221.	Study outcome does not fulfill outcome definition (i.e. PECO)
Sauni R.; Uitti J.; Jauhiainen M.; Kreiss K.; Sigsgaard T.; Verbeek JH. Remediating buildings damaged by dampness and mould for preventing or reducing respiratory tract symptoms, infections and asthma (Review). Evidence-based child health : a Cochrane review journal May 2013;8(3):944-1000.	Study outcome does not fulfill outcome definition (i.e. PECO)
Sauni R.; Uitti J.; Jauhiainen M.; Kreiss K.; Sigsgaard T.; Verbeek JH. Remediating buildings damaged by dampness and mould for preventing or reducing respiratory tract symptoms, infections and asthma. The Cochrane database of systematic reviews Sep 2011;(9):CD007897.	Study outcome does not fulfill outcome definition (i.e. PECO)
Sauni, Riitta; Verbeek, Jos H.; Uitti, Jukka; Jauhiainen, Merja; Kreiss, Kathleen; Sigsgaard, Torben. Remediating buildings damaged by dampness and mould for preventing or reducing respiratory tract symptoms, infections and asthma. Cochrane Database of Systematic Reviews 2015;(2):CD007897-CD007897.	Study outcome does not fulfill outcome definition (i.e. PECO)
Schweigert MK.; Mackenzie DP.; Sarlo K. Occupational asthma and allergy associated with the use of enzymes in the detergent industry-a review of the epidemiology, toxicology and methods of prevention. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology Nov 2000;30(11):1511-8.	Other reason (e.g. not a systematic review)
Soyseth, Vidar; Johnsen, Helle L.; Kongerud, Johny. Respiratory hazards of metal smelting.Current opinion in pulmonary medicine 2013;19(2):158-162.	Other reason (e.g. not a systematic review)
van Kampen, V.; Merget, R.; Baur, X. Occupational airway sensitizers:	Other reason (e.g.

An overview on the respective literature. American Journal of Industrial Medicine 2000;38(2):164-218.	not a systematic review)
Vandenplas, Olivier; Raulf, Monika. Occupational Latex Allergy: the Current State of Affairs. Current Allergy and Asthma Reports 2017;17(3):14-14.	Other reason (e.g. not a systematic review)
Wiggans R.E.; Evans G.; Fishwick D.; Barber C. Respiratory ill health in the furniture and wood processing industries: A systematic review European Respiratory Journal / 2015;46	Other reason (e.g. not a systematic review)

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PAPER II

The relation between potential occupational sensitizing exposures and asthma: a systematic review

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ABSTRACT

Introduction: Based on the knowledge gap identified in a recent overview of systematic reviews we aimed to conduct a systematic review of the relation between 10 selected potential occupational sensitizing exposures and asthma.

Materials and methods: We conducted a systematic literature search in three databases for peer-reviewed studies published between July 2011 and August 2019. Criteria for eligibility included 10 potential occupational sensitizing exposures (amines, anhydrides, biocides, crustaceans, enzymes, mammals, metals, "mould, fungi and yeast", molluscs, and other chemicals) previously classified as having no or limited evidence of a relation with asthma. Study selection, data extraction, and risk of bias assessment were conducted by two reviewers. Based on the quality and quantity of the included studies, we upgraded or downgraded the level of evidence for main groups and subgroups/specific exposures.

Results: Thirty-seven studies were included in the present review. The overall confidence in study results was rated high in five, moderate in 13, and low in 19 studies. No studies published after 2011 were found for amines, anhydrides, and molluscs. For the seven studied potential occupational sensitizing exposures, we upgraded main groups of crustaceans and enzymes to moderate evidence, while main groups of mammals, metals, and "mould, fungi and yeast" were upgraded to limited or contradictory evidence. For subgroups/specific exposures, pesticides, cleaning agents (i.e., chloramine and disinfection products), and an unspecified group of other chemicals (i.e., acrylates) were upgraded to moderate evidence.

Conclusion: This systematic review provided an updated list of potential occupational sensitizing exposures able to cause asthma.

BACKGROUND

Asthma is a common chronic disease among both children and adults with symptoms like coughing, shortness of breath, and wheezing caused by variable airflow obstruction. The disease is characterized by airway inflammation and hyper-responsiveness, leading to variable degree of airway re-modelling.[1] It is estimated that 15 % of adult asthma is related to occupational exposures.[2, 3]

Asthma caused by occupational exposures is mostly considered to be due to specific immunological mechanisms, either driven by IgE-mediated sensitization or other less well characterized immunological mechanisms.[4, 5] The relation between potential occupational sensitizing exposures and asthma has been reported in hundreds of studies with a wide range of exposures. In addition, numerous reviews have been published, but the vast majority is scoping reviews or discussion papers. In a comprehensive systematic review of 372 potential occupational sensitizing exposures, Baur *et. al.* (2014) found strong evidence of a relation for exposure to various laboratory animals, moderate evidence for 35 exposures, and limited or no evidence for the remaining exposures.[6] We recently conducted an overview of systematic reviews including 1189 studies of 486 potential occupational sensitizing exposures (Dalbøge et.al. *in draft*). In this overview, we found strong evidence of a relation for main groups of wood dusts, and moderate evidence for main groups of mites and fish. For subgroups/specific exposures, we found strong evidence for exposure to laboratory animals, and moderate evidence for 55 subgroups/specific exposures. For the remaining exposures, limited/contradictory or no evidence was found.

The aim of this study was to conduct a systematic review of the relation between asthma and 10 potential occupational sensitizing exposures previously classified as having no or limited evidence i.e.,

amines, anhydrides, biocides, crustaceans, enzymes, mammals, metals, "mould, fungi and yeast", molluscs, and other chemicals.

MATERIALS AND METHODS

Protocol and registration

This study was the second of two studies of the relation between potential occupational sensitizing exposures and asthma requested by The National Board of Industrial Injuries and the Occupational Diseases Committee in Denmark. Our study protocol was registered in PROSPERO (CRD42017057014). We followed specific guidelines for preparation and quality approval provided by the Danish Work Environment Fund and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[7]

Literature search, eligible criteria and exclusion of studies

We constructed a PECO (Population, Exposure, Comparison, Outcome) for study eligibility (appendix 1). The population included persons in or above working age, 10 potential occupational sensitizing exposures, a comparison between occupational sensitizing exposures and asthma, and self-reported or clinically assessed asthma. The 10 potential occupational sensitizing exposures were selected among groups of sensitizing exposures with no scientific to limited evidence of a relation found in our overview of systematic reviews (Dalbøge et.al. *in draft*). We prioritized frequent potential occupational sensitizing exposures, suspected low molecular weight exposures, and exposures which are not considered well known causes of asthma. The 10 selected sensitizing exposures included amines, anhydrides (not Phthalic anhydride), biocides, crustaceans (not lobsters and snow crabs), enzymes (not a-amylase from *Aspergillus oryzae*, detergent enzymes, Papain, Phytase from

Aspergillus niger, various enzymes from *Bacillus subtilis* (alcalase, protease, maxatase, maxapem, esperase, cellulase, a-amylase, lipase, subtilisin), mammals (not cows, rats), metals (not Platinum salts), mould, fungi and yeast (not *Aspergillus, Cladosporium, Penicillium*), molluscs, and other chemicals (not drugs, dyes, biocides, and isocyanates). The exposures in parenthesis were excluded as we found moderate to strong evidence of a relation for these subgroups/specific exposures in our overview. "Other chemicals" is considered a subgroup of chemicals, and are not strictly defined but contain highly reactive chemicals like disinfections, acrylates, epoxy resin, and persulfates. In order to disentangle the effect of specific cleaning agents, we decided to include cleaning agents under other chemicals, even though moderate evidence for unspecific cleaning agents was documented in our overview. To be as comprehensive as possible, we did not exclude studies of exposures, which is considered a mixture of possible sensitizing exposure and other types of exposures e.g., metal fluid. Eligible studies included epidemiological (e.g., cross-sectional, case-control, and cohort studies) as well as clinical studies (e.g., case-reports and case-series).

In collaboration with a librarian, the literature search was conducted in three databases i.e., the National Library of Medicine (MEDLINE/PubMed), Embase, and Web of Science (WoS) (appendix 2) for peer-reviewed studies published between the 1st of January 2011 and 29th of august 2019; July 2011 was the date of the literature search in Baurs review.[6] In Covidence (https://www.covidence.org), article duplicates and studies published before July 2011 were excluded. Two reviewers independently excluded studies based on title/abstract screening and full paper reading (appendix 3). Disagreement was resolved by consensus. Several studies were well known to some of the review authors, so we did not blind for authorship. We screened the reference lists of all included studies for additional relevant articles.

Data extraction and risk of bias assessment for each study

For each included study, two reviewers extracted information on e.g., study design, population, outcome, exposure, confounders, and exposure-response relation. The methodological quality of each included study was independently assessed by two reviewers using a "risk of bias" tool developed for this study. This tool included 10 items; item 1-9 concerned study design, population, participation rate, exposure specificity, exposure assessment (I-II), outcome assessment, confounders adjusted for, and exposure-response relation, which could be scored "high" or "low". Item 10 was a subjective rating of the overall confidence in study results based on item 1-9. The overall confidence could be scored "high", "moderate", "low" or "critically low" (appendix 4). Disagreement on item quality was resolved by a third reviewer (AD or VS). For two random selected studies (i.e., an observational study and a case report), all reviewers pilot-tested the risk of bias tool, discussed disagreements, and reached consensus.

Quality of evidence of a relation across studies

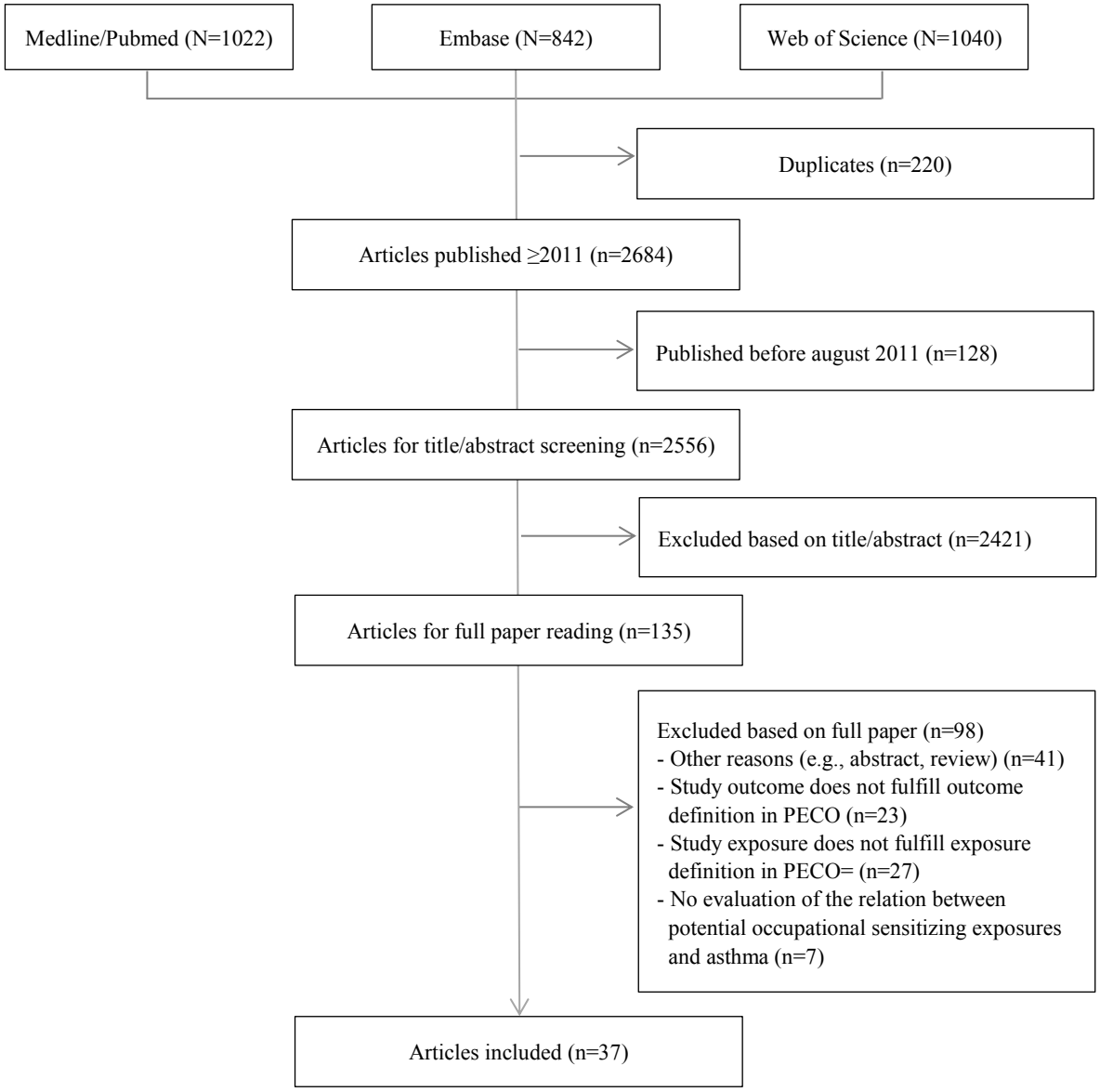
For each study, we extracted information of the relation between potential occupational sensitizing exposures and asthma for both main groups (e.g., mammals) and subgroups/specific exposures (e.g., mouse). Two reviewers (AD and VS) upgraded or downgraded the level of evidence for main and subgroups/specific exposures found in our overview of systematic review (Dalbøge et. al. *in draft*) using a modification of the Royal College of General Practitioners (RCGP) three-star system of the British Occupational Health Research Foundation (appendix 5).[6, 8]

RESULTS

Literature search and exclusion of studies

A flow chart of the literature search and exclusion of articles based on eligibility is presented in figure 1. A total of 2904 articles were identified from the three databases. We excluded 220 duplicates and 128 articles published before July 2011. After title/abstract screening and full paper reading, we excluded additional 2421 and 98 articles, leading to 37 articles fulfilling the criteria for inclusion in the present review. Appendix 6 lists the 98 excluded articles and the explanation for their exclusion.

Figure 1. Flow chart of the literature search and exclusion of studies



Study characteristic and risk of bias

Study characteristic and risk of bias of the 37 included studies are presented in table 1. Seven cohort studies, three case-control studies, 10 cross-sectional studies, and 17 case-reports or case-series were included. The overall confidence in study results was rated high in five studies, moderate in 13 studies, and low in 19 studies. For epidemiological studies, overall confidence in study results was rated moderate in six studies, and low in 14 studies. For clinical studies, overall confidence in study results was rated high in five, moderate in seven, and low in five studies. Among all 37 studies, the most frequent items scoring "high" were assessment of potential information bias, exposure specificity, and objective measurement of variability of lung function. The most frequent items scored "low" were assessment of risk factors for incident asthma, assessment of exposure-response relation, and adjustment of specific confounders. The source of funding for each of the included reviews was evaluated but not reported.

Table 1. Description of the 37 included studies published between 2011 and 2019

Author	Study design	Population	Participation rate	Exposure		Outcome	Confounders adjusted for	Exposure-response analysis	Study quality
				Definition	Assessment	Assessment			
	1	2	3	4	5, 6	7	8	9	10
Baur, 2013[9]	Case-report	60-year old male chemical worker in the production and packaging of detergents for 32 years (N=1)	100 %	*Enzymes:* Bacterial alpha-amylase termamyl	Self-report and expert assessment	History of work-related asthma symptoms, lung-function test (FEV_1/FVC with or without bronchodilator), IgE measurement (Savinase, Termamyl, alkalase, cellulase, fungal alpha-amylase, total), SPT (common allergens)	Self-control	No	
Risk of bias	0	0	0	1	0, 1	1	0	0	Low
Beach, 2012[10]	Cohort	Male and females with a claim to Workers' Compensation Board (N=11 486)	83 %	*Different exposures:* 8 HMW agents, 4 LMW agents, 3 mixed agents (e.g., animal antigens, cleaning products, shellfish, latex, metal and fumes, metal working fluids)	Register information on occupational code combined with an expert-based JEM	Physician billing for asthma (ICD-9 493) 12 months before a Workers' Compensation Board claim without asthma previous years	Cases and referents matched by age, date of the case claim, prior number of claims, sex	No	
Risk of bias	0	1	1	0	1, 0	0	0	0	Low
Bertelsen, 2016[11]	Case-report	48-year old female worker in a plant producing marine savory seafood ingredients (N=1)	100 %	*Crustaceans:* Shellfish powder (shrimp)	Self-report and expert assessment. Non-blinded SIC; control exposure lactose powder (placebo), active exposure shellfish powder from the plant	History of work-related asthma symptoms, lung function tests (FEV_1, FVC, FEV_1/FVC, PEF, FeNO, DLCO, methacholine provocation test), IS, IgA, IgE, IgM, IgG measurements (food allergens, shrimp, total), IgE for common allergens (Phadiatop), total IgE	Self-control	Yes	
Risk of bias	1	0	0	1	0, 1	1	1	1	High
Cha, 2012[12]	CS	Male and female self-employed farmers near an oil spill (N=2882)	NS	*Pesticide:* Paraquat (1,1'-dimethyl-4,4' bipyridinium dichloride)	Interview	Questionnaire: Asthma defined in terms of the subject having ever been diagnosed with the disease by a physician	Age, alcohol, education, cumulative exposure of three pesticides, distance from oil spill site, sex, smoking	No	
Risk of bias	0	0	0	1	0, 1	0	0	0	Low
Dumas, 2014[13]	CS	Estonian male and female workers aged 18-65 from population-based biobank, patients	88.3 %	*Different:* 18 known asthmagens and 4 known work irritant environments (eg., animals, enzymes,	Longest held job combined with a asthma-specific JEM	Interviews by medical personnel: "Do you have asthma now", asthma confirmed by physician, health status and medication	Age, sex, smoking	No	

		and volunteers from media campaign (N=34 015)		latex, highly reactive chemicals, cleaning/ disinfecting products, metals)					
Risk of bias	0	0	1	0	1, 0	0	0	0	Low
Ghosh, 2013[14]	Cohort	Male and females who participated in the National Child Development Study, born 3-9 March, 1958 (N=7406)	NS	*Different:* 18 high-risk workplace substances; animal antigens, shellfish, antigenic enzymes, highly reactive chemicals, cleaning products, metal and metal fume antigens, reactive chemicals, cleaning products, metal fumes	Self-reported job history (interview) combined with an asthma-specific expert-based JEM	At age 44-45: Lung-function test (FEV_1/FVC), IgE (total, dust, cat, grass). Interview: Self-reported adult onset asthma, self-reported adult asthma and self-reported adult asthma with obstruction (FEV_1/FVC<70).	Father's social class at birth, hay fever, region, sex	No	
Risk of bias	0	1	0	0	1, 0	1	0	0	Low
Gonzalez, 2014[15]	CS	Male and female healthcare workers age 18-65 of years i.e., physicians, nurses, cleaners, radiological technicians, physiotherapist, administrative personnel (N=543)	77 %	*Other chemicals:* Cleaning products i.e., chlorinated/bleach, cleaning/disinfection-related chemicals, glutaraldehyde, latex gloves, quaternary ammonium compounds	Questionnaire, material data sheets, workplace observations	Self-reported physician diagnosed asthma ("Have you ever had asthma" and "Was it confirmed by a doctor"), respiratory symptoms, IgE measurements (e.g., latex, quaternary ammonium compounds)	Age, atopy, BMI, chlorinated/bleach, latex gloves, sex, smoking, quaternary ammonium compounds	No	
Risk of bias	0	0	1	1	0, 1	0	1	0	Moderate
Helaskoski, 2014[16]	Case-series	Male and female patients (25-52 years of age) from occupational medicine clinic (N=5)	100 %	*Hair dressing products* e.g., persulfates, permanent wave solutions, hair bleach	Questionnaire, SIC (lactose powder, oxidative hair dyes, not blinded)	History of respiratory symptoms, lung-function test (FEV_1, PEF, histamine challenge, peak flow at/off work, FeNO), IgE measurements (total), SPT (common environmental allergens, most common hairdresser chemicals e.g., oxidative hair dyes), open skin testing (hair dye products), patch test (hairdresser chemicals)	Self-control	No	
Risk of bias	1	0	0	1	0, 1	1	1	0	Moderate
Hougaard, 2012[17]	Case-report	18 year-old female hairdressing apprentice; apprenticeship for 2 years (N=1)	100 %	*Other chemicals:* Persulfate salts (potassium persulfate and ammonium persulfate)	Self-report and expert assessment	History of work-related asthma symptoms, lung-function test (daily PEF), SPT (common allergens, hairdressing series i.e., potassium persulfate and ammonium persulfate), patch teat (standard series, hairdressing series)	Self-control	No	
Risk of bias	0	0	0	1	0, 1	1	0	0	Low
Hoy, 2013[18]	Cohort	Male and female school children of 7-10 years of age (N=792)	NS	*Different exposures:* Eighteen different occupational agents e.g. latex, shellfish,	Self-reported job history combined with an asthma-specific JEM	Questionnaire: Asthma at the age of 44 defined as "Have you ever in your life suffered from attacks of asthma or wheezy breathing?	Sex, smoking	Yes (latex)	

				enzymes, highly reactive chemicals, industrial cleaning agents, metal sensitizers, metal working fluids					
Risk of bias	0	1	0	0	0, 1	0	0	1	Low
Huang, 2016[19]	CC	Male and female adults with adult-onset asthma enrolled from a general hospital. Controls sampled living in the same residential area (N=1102)	NS	*Metals:* Al, As, Ba, Cd, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pb, Rb, Sb, Se, Sn, Sr, Ti, U, V, W, Zn	Interview, urinary measurements (metals)	History of asthma symptoms, physician-diagnosed asthma, lung-function test (daily spirometry, FEV_1,FEV_1/FVC)	Age and sex-matched, BMI, education, occupational dust, family history of asthma, smoking, pets, flower gardening, physical activity	No	
Risk of bias	0	0	0	1	1, 1	1	1	0	Moderate
Jungewelter, 2019[20]	Case-report	35-year-old female slaughterhouse worker; patient A (N=1)	100 %	*Mammals:* Raw pork meat and kidney	Self-report and expert assessment. SIC (minced raw pork meat and kidney, handling iceberg lettuce, not blinded)	History of work-related asthma symptoms, lung-function test (FEV_1, FeNO, PEF, histamine), IgE measurements (pig urine protein), SPT (raw pork meat, pork kidney, pig dander, common aeroallergens)	Self-control	No	
Risk of bias	1	0	0	1	0, 1	1	0	0	Moderate
Lastovkova, 2015[21]	Case series	Male and female patients 33-62 years of age from Czech heat-exchanger production line (N=5)	100 %	*Other chemical*: potassium aluminium tetrafluoride	Workplace measurement of air concentration, SIC (potassium aluminium tetrafluoride powder from the workplace), provocation at workplace (no blinding or sham)	Lung-function test (FEV_1, PEF, MEF, FeNo, non-specific broncho-provocation with histamine or methacholine, bronchodilatation with salbutamol, total airway restiance), IgE measurements (total)	Self-control	No	
Risk of bias	1	0	0	1	0, 1	1	0	0	Moderate
Le Moual, 2012[22]	CS	Enriched female with asthma recruited from a chest clinics, their relatives, group of population-based subjects (N=683)	41.2 %	*Other chemicals:* 24 domestic cleaning exposures (9 cleaning tasks, 15 cleaning agents)	Self-report (questionnaire), component analysis	Asthma symptoms, lung-function test (FEV_1 methacholin challenge test), IgE measurements (total), SPT (12 allergens)	Age, BMI, education level, occupational exposures, smoking	No	
Risk of bias	0	0	0	0	0, 1	1	0	1	Low
Lillienberg, 2013[23]	Cohort	Male and female random sampled from the general Nordic population from seven geographic centres	74 %	*Different exposures:* e.g., acrylates, cleaning products, reactive chemicals, metal working fluids	Self-reported job history combined with an asthma-specific expert-based JEM	Questionnaire: "Do you have or have you ever had asthma after the age of 16" and "Have you ever had asthma diagnosed by a physician"	Age, atopy	No	

		(born 1945-1973) (N=13.284)							
Risk of bias	0	1	1	0	1, 0	0	0	0	Low
Lillienberg, 2014[24]	Cohort	Male and female random sampled from the general Nordic population from seven geographic centres (born 1945-1973) (N=13.284)	74 %	*Different exposures:* e.g., acrylates, cleaning products, reactive chemicals, metal working fluids, highly reactive chemicals	Self-reported job history combined with two asthma-specific expert-based JEM	Questionnaire: "Do you have or have you ever had asthma after the age of 16" and "Have you ever had asthma diagnosed by a physician"	Age, atopy	No	
Risk of bias	0	1	1	0	1, 0	0	0	0	Low
Lipinska-Ojrzanowska, 2013[25]	Case-report	51-year-old female process operator in dishwashing tablets factory for 4 years (N=1)	100 %	*Enzymes:* Savinase	Self-reported exposure to cleaning agents, material data sheets. Single blinded SIC; control exposure talcum, active exposure powder of crushed dishwashing tablets	History of work-related asthma symptoms, lung function tests (FEV1, FVC, FEV1/FVC, PEF, methacholine inhalation challenge test), IgE measurements (savinase, total), SPT (common allergens, alfa-amylase)	Self-control	No	
Risk of bias	1	0	0	1	1, 1	1	1	0	High
Lipinska-Ojrzanowska, 2017[26]	Case-series	Female professional cleaners referred for suspected asthma (N=50)	100 %	*Other chemicals:* cleaning agents e.g., latex and disinfectants	Self-reported exposure to cleaning agents, material data sheets. SIC: placebo, vinyl gloves, NaCl, latex gloves, cleaning agents e.g., disinfectants, no sham	History of work-related symptoms, lung-function test (FEV_1, FVC FEV_1/FVC, PEF with our without salbutamol /methacholine), IS, IgE measurements (total and specific i.e., latex, cleaning agents), SPT (common allergens, latex, cleaning agents)	Self-control	No	
Risk of bias	1	0	0	1	0, 1	1	0	0	Moderate
Liu, 2019[27]	CS	Population-based sample of plastic film greenhouse workers (N=5420)	92.2 %	*Other chemicals:* Pesticide use; type of green house (vegetables, flowers, poultry, mushroom); foul greenhouse odors	Self-report (interview)	History respiratory symptoms, lung-function test (FEV_1/FVC, postbronchodilator test with salbutamol)	NS	No	
Risk of bias	0	0	1	0	0, 1	1	0	0	Low
Moore, 2016[28]	Case-series	Domestic cleaners and healthcare workers (N=4)	100 %	*Other chemicals:* Chlorine-releasing tablets (i.e., chlorine, urine, mix of chlorine and urine (chloramine)	SIC; neutral detergent solution, chlorine-releasing tablets, Haztabs, urine, mix of chlorine and urine, no sham	Lung-funtion test (FEV_1 with/ without metacholine, FVC, whole day PEF for four week, FeNO pre and post each challenge test, non-specific bronchoprovocation), IgE measurements (e.g., latex)	Own control	No	
Risk of bias	1	0	0	1	0, 1	1	0	0	Moderate

Oppliger, 2017[29]	Cohort	Laboratory animal workers and students e.g., faculties of medicine, veterinary, medicine and science (N=177)	58,6 %	*Mammals:* Rat and mouse antigens, endotoxin	Questionnaire (interview), personal workplace measurements (airborne dust)	History of symptoms, lung-function test (e.g., FEV_1, FVC, FEV_1/FVC), IgE measurements (total, mouse, rat)	BMI, education, nationality, sex, smoking	No	
Risk of bias	0	0	0	1	1, 1	1	0	0	Moderate
Patel, 2018[30]	CS	Active primary farm operators; responsible for running the farm (N=11 210)	70.8 %	*Other chemicals:* Pesticides herbicides, phenoxy, 2,4-D, glyphosate, insecticides	Questionnaire and information on active ingredients obtain through product research page	Physician diagnosed asthma and still symptoms (current asthma)	Region, sex	No	
Risk of bias	0	0	1	1	0, 1	0	0	0	Low
Pravettoni, 2014[31]	Case-report	41-year-old female food industry worker (e.g., packaging of various dried mushrooms) (N=1)	100 %	Mushrooms: shiitake mushrooms (Lentinus edodes)	Self-report and expert assessment	History of work-related asthma symptoms, lung-function tests (FEV_1, FVC with/without bronchodilator (salbutamol)), FeNO, SDS-PAGE, IgE-immunoblotting, IgE measurements (total, moulds: Aspergillus fumigatus, Alternaria alternate, Penicillum notatum, Cladosporium herbarum, champignon: Agaricus bisporus), SPT (commercial aeroallergens, food allergens e.g., mushrooms, negative controls)	Self-control	No	
Risk of bias	0	0	0	1	0, 1	1	0	0	Low
Roussel, 2012[32]	CS	Archive workers from 10 archive centers (N=144)	54 %	*Moulds fungi or yeast;* specific penicillium (i.e., Cladosporium sphaerospermum, Alternaria alternata, Stachybotrys chartarum, Aspergillus fumigatus)	Measurements; Air and dust samples in the 10 archive centers (e.g., moulds), questionnaire	Self-reported physician diagnosed asthma	Age, sex, smoking	No	
Risk of bias	0	0	0	1	1, 1	0	0	0	Low
Simoneti, 2016[33]	CS	Male and female workers or students at two universities dealing/working with/without laboratory animals (N=737)	95 %	*Mammals:* Lab animals (i.e., rat, rabbit, mouse, hamster, guinea-pig)	Self-report, dust samples from work room floor (e.g., mouse and rat allergens)	History of respiratory symptoms, lung-function tests (FEV_1, bronchial challenge test with mannitol), SPT (common allergens, laboratory animals i.e., rat, rabbit, mouse, hamster, guinea pig)	Age, concentration of allergens, daily work hours, exposure years, groups, institution, job category, past exposure, pet ownership, sex, smoking	Yes	
Risk of bias	0	0	1	1	1, 1	1	0	1	High
Simoneti, 2017[34]	CS	Male and female students and	95 %	*Mammals:* Laboratory animals (rat, rabbit,	Self-reports and dust samples from	History of respiratory symptoms, lung-function tests (FEV_1, bronchial	Age, daily work hours, exposure	Yes	

		employees at 2 universities dealing/working with laboratory animals (N=453)		mouse, hamster, and guinea-pig)	work room floor analyzed for endotoxin	challenge test with mannitol), SPT (common allergens, laboratory animals i.e., rat, rabbit, mouse, hamster, guinea pig)	years, pet ownership, sex, smoking		
Risk of bias	0	0	1	1	0, 1	1	0	1	Moderate
Singh, 2013[35]	CS	Male and female dental healthcare workers and students, and non-clinical staff from 5 academic dental institutions (N=454)	NS	*Other chemicals:* Dental spray, mist or stem, latex	Self-reports	Questionnaire: "Have you had an attack of asthma in the last 12 months" and "Are you currently taking any medication for asthma", lung-function test (FEV_1, FVC, bronchodilator), IgE measurement (common inhalants, latex, horse radish peroxidase, bromelain)	Age, sex, smoking	No	
Risk of bias	0	0	0	1	0, 1	1	0	0	Low
Song, 2013[36]	Case-report	34-year old male wallpaper manufacturer (N=1)	100 %	*Other chemicals* Polyvinyl Chloride (PVC) *Metals:* Nickel	PVC and stone powder handled at workplace, no measurements, SIC (PVC, nickel), no blinding or sham	History of respiratory symptoms, lung-function test (FeNo, FEV1, methacholin challenge test, bronchial challenge test; saline, PVC), IgE measurements (total), SPT (common allergens, intradermal test (PVC)), patch test (PVC, zinc oxide, Nickel, chromium), sputum eosinophils	Self-control	No	
Risk of bias	1	0	0	1	0, 1	1	0	0	Moderate
Suojalehto, 2018[37]	Case-reports	Factory workers exposed to 3-(Bromomethyl)-2chloro-4(methylsulfonyl)-benzoic acid office worker at the same factory (N=93)	92 %	*Other chemicals:* 3-(Bromomethyl)-2chloro-4(methylsulfonyl)-benzoic acid (BCMBA)	Questionnaire, interview, dust measurements, observations, SIC (3-(Bromomethyl)-2chloro-4(methylsulfonyl)-benzoic acid, control powder; lactose powder)	History of respiratory symptoms, lung-function test (spirometry; FEV_1, histamine challenge, FeNO), IgE measurements (total), SPT (common allergens, Alternaria alternate, Cladosporium herbarum, 3-(Bromomethyl)-2chloro-4(methylsulfonyl)-benzoic acid), open skin application test (3-(Bromomethyl)-2chloro-4(methylsulfonyl)-benzoic acid)	Self-control	Yes	
Risk of bias	1	0	0	1	0, 1	1	1	1	High
Suojalehto, 2019[38]	Case-reports	Referred patients with suspected asthma and working with epoxy resins or triglycidylether (N=113)	100 %	*Other chemicals:* Epoxy resin, polyamine hardeners, triglycidyl isocyanurate (TGIC)	Work place measurements (airborne polyamines and solvents, amines). SIC (butyl acetate solvent, 1-component, solvent-based paint, lactose.powder, epoxy resin, polyamine hardener, triglycidyl isocyanurate)	Symptoms, lung-function test (FeNO, FEV_1, histamine/methacholine, placebo), SPT (serum albumin-conjugated diglyirid eher of bisphenol A epoxy resin, epoxy components)	Self-control	No	

Risk of bias	1	0	0	1	0, 1	1	1	0	Moderate
Vandenplas, 2013[39]	Case series	Cleaners who completed a SIC procedure with cleaning agents in a tertiary centre (N=44)	100 %	*Other chemicals:* cleaning agents e.g., quaternary ammonium compounds, glutar-aldehyde, both of these agents and ethanolamines	Interview, data sheets, experts assessment, SIC; open SIC (control with paint diluent, cleaning products)	Lung-function test (spirometry; FEV_1, sputum eosinophils, histamine bronchial reactivity), sputum cell counts	Self-control	Yes	
Risk of bias	1	0	0	1	0, 1	1	1	1	High
Vincent, 2018[40]	CC	Asthma patients with and without mould sensitization (N=64)	100 %	*Mould, fungi, yeast:* Alternaria alternata, Cladosporium herbarum, Aspergillus fumigatus, Penicillium spp, Cladosporium sphaerospermum, Cladosporium cladosporioides, Aspergillus versicolor contamination in dwellings	Questionnaire, mould contamination assessed and measured in main rooms at home	History of respiratory symptoms, lung-function test (FEV_1, FVC, FEV_1/FVC) IgE measurements (total, specific moulds), SPT or cellulose acetate membrane precipitin to moulds (histamine, codeine, A fumigatus, A alternata,Penicillium chrysogenum, and Cherbarum)	Age, sex, smoking	No	
Risk of bias	0	0	0	1	1, 1	1	0	0	Moderate
Vizcaya, 2013[41]	CC	Male and female cleaners with and without asthma from 37 cleaning companies (N=95)	49.7 %	*Other chemicals:* Cleaning products e.g., ammonia, bleach, degreasers, drain products, dust mop products, glass cleaners, hydrochloric acid	Interview	History of respiratory symptoms, lung-function test (FeNo, methacholine challenge test, exhaled breath condensate spirometry with or without salbutamol; FEV_1, FVC, FEF25-75%) IgE measurements (common aeroallergens, dust mites, latex)	Age, domestic use of cleaning product, sex, smoking	No	
Risk of bias	0	0	0	1	0, 1	1	0	0	Low
Walters, 2017[42]	Case-series	Male and female workers in a variety of industries e.g. manufacturing, health care, education, hair and beauty, printing (n=20)	100 %	*Other chemicals:* Acrylates, acrylic co-polymers, methyl methacrylates	Medical/hygiene reporting from companies, SIC (specific allergens e.g., acrylates (N=11 % of cases)	History of respiratory symptoms, lung-function test (FEV1, FVC, FeNO, PEF, non-specific bronchial reactivity (N=70 %)), IgE measurements (specific allergens (N=46%)), SPT (e.g., common allergens, acrylates)	Self-control	No	
Risk of bias	1	0	0	1	0, 1	1	0	0	Low
Walters, 2018[43]	Case-series	Clinical patients e.g., lifeguards and swimming pool employee, nurses, healthcare cleaner, healthcare assistants, hard hostess, psychiatric ward housekeeper (N=80)	100 %	*Other chemicals:* Cleaning agents e.g., chloramines, glutaraldehyde, quaternary ammonium compounds	Medical/hygiene reporting from companies, SIC (specific cleaning agents (N=11 % of cases)	History of respiratory symptoms, lung-function test (FEV1, FVC, FeNO,PEF, non-specific bronchial reactivity (N=70 %)), IgE measurements (specific allergens (N=46%)), SPT (e.g., common allergens, acrylates)	Self-control	No	

Risk of bias	1	0	0	1	0, 1	1	0	0	Low
Weinmann, 2017[44]	Cohort	Male and female 19-24 year, population based cohort, two German study centers (N=1695)	22.6 %	*Other chemicals:* Cleaning products (i.e., domestic disinfectants; household sprays)	Questionnaire	Questionnaire: physician-diagnosed asthma and either wheezing without cold or use of asthma medication within the last 12 mounts	Age, sex, socioeconomic status, smoking, study centre	Yes	
Risk of bias	0	1	0	0	0, 1	0	0	1	Low
Wittczak, 2013[45]	Case-reports	46-year old female nurse in internal medicine ward, 34-year old female nurse in pediatric nephrology ward, 45 year-old female nurse in cardiology (N=3)	100 %	Other chemicals: Chlorhexidine	Exposure assessment not specified, single-blind, placebo-controlled SIC (linen oil, chlorhexidine)	Lung-function test (spirometry, FEV1, FVC, P20, methacholine challenge test),IgE measuremts (total, chlorhexidine, natural rubber latex), SPT (common aeroallergens, chlorhexidine), sputum	Self-control	Yes	
Risk of bias	1	0	0	1	1, 1	1	1	0	High

BMI; Body Mass Index, CC; Case-control study, CS; Cross-sectional study; DLCO; Carbon monoxide diffusing capacity of the lung, FEV1; Forced expiratory volume in one second, FEF25-75; Forced expiratory flow over the middle half of FVC, FeNO; Fractional exhaled nitric oxide, FVC; Forced vital capacity, HMW; High molecular weight, IgE; Immunoglobulin E, IS; induced sputum, JEM; Job exposure matrix, LMW; Low molecular weight, MEF; Mean expiratory flow, NS; Not specified, SPT; Skin-prick test, SIC; Specific inhalation challenge

Relation between potential occupational sensitizing exposures and asthma

The measure of association for each study is presented in table 2. The table also presents the risk of bias assessment for each study, the *a priori* level of evidence based on the overview of systematic reviews, and the current level of evidence based on the included studies in this review according to the RCGP system. The level of evidence for subgroups/specific exposures is only presented, if the relation was moderate to strong. As no studies were identified for amines, anhydrides, and molluscs, the following section describes the results for the seven studied exposures.

Biocides

Biocides were studied in three low quality-rated studies covering eight pesticides.[12, 27, 30] For four pesticides, statistically significant associations were found (i.e., any pesticide use, herbicides, insecticides, and multiple pesticides),[27, 30] while non-statistically significant associations were found for the remaining four pesticides (i.e., glyphosate, paraquat (1,1'-dimethyl-4,4' bipyridinium dichloride), phenoxy, and 2,4-D).[12, 30] In our overview of systematic reviews, we found no evidence of a relation for biocides, and limited/contradictory evidence for pesticides. Based on the three studies identified in this systematic review, the level of evidence remained unchanged for biocides (i.e., no evidence), while we upgraded the level of evidence for pesticides from limited/contradictory to moderate.

Crustaceans

Crustaceans (only shellfish) were studied in four studies with low to high quality-rating.[10, 11, 14, 18] A statistically significant association was found for fish/shellfish in one study,[10] an association was concluded for shellfish powder in a case-report,[11] an incidence proportion of 12.5 was found in one

study,[14] while another study found no statistically significant association.[18] Based on new studies, we upgraded the level of evidence from limited/contradictory to moderate.

Enzymes

Six studies with quality rating varying from low to high included six enzymes.[9, 13, 14, 18, 24, 25] Statistically significant associations was found for two enzymes (i.e., antigenic enzymes and enzymes),[13, 14] two case-reports found that Bacterial alpha-Amylase termamyl and savinase caused asthma,[9, 25] and a non-statistically significant association was found for two enzymes (i.e., bioaerosol enzymes and enzymes).[18, 24] Based on the new studies, the level of evidence was upgraded to moderate.

Mammals

Eight studies on eight mammals with quality rating varying from low to high were included (four studies of animals).[10, 13, 14, 18, 20, 29, 33, 34] A statistically significant association was found for lab animals,[34] one study found that "rat or mouse" exposure caused asthma in six persons,[29] a case-report concluded that raw pork meat caused asthma in one persion,[20] while no statistically significant association was found for mouse allergens.[33] Based on studies of mammals, we changed the level of evidence from no scientific to limited/contradictory evidence.

Metals

Eight studies with quality rating varying between low and moderate, studied nine main groups of metal and 14 specific metals.[10, 13, 14, 18, 19, 23, 24, 36] The nine groups of metal were studied in six studies[10, 13, 14, 18, 23, 24] with statistically significant associations found for three exposure groups (i.e., "metal and metal fume", "metal and metal fume antigens", and metal sensitizers),[10, 14] a non-statistically significant

association was found for "metal and metal fume antigens",[24] while no statistically significant association was found for five exposure groups (i.e., metal, metal sensitizers, and metal working fluids).[13, 14, 18, 23] For specific metals, statistically significant increase in risks was found for seven of the 14 metals (i.e., Cd, Cr, Cu, Mo, Ni, Se, U).[19, 36] Based on new studies, we upgraded the level of evidence for metals from no evidence to limited/contradictory evidence.

Mould, fungi and yeast

Mould, fungi and yeast were studied in three low quality-rated studies including five exposures.[31, 32, 40] Shitake mushrooms was found to cause asthma in a case-report,[31] a non-statistically significant association was found for "contact with mouldy documents" and "fungi in arhieves",[32] while no statistically significant associations were found for two exposures (i.e., *Alternaria alternata* and "fungi in archives").[32, 40] Based on the new studies, we upgraded the level of evidence from no scientific to limited/contradictory evidence.

Other chemicals

Other chemicals were studied in 22 studies, which included 90 chemicals; study quality varied between low and high. We divided other chemicals into three subgroups i.e., cleaning agents, highly reactive chemicals, and an unspecified group of other chemicals.

Cleaning agents: Seventy-two cleaning agents were studied in 15 studies with study quality ranging from low to high.[10, 13-15, 18, 22-24, 26, 28, 35, 39, 41, 43, 44] Statistically significant associations were found for 10 exposures,[14, 15, 22-24, 26, 28, 39, 43, 44] an association was found for 23 agents in case-studies,[23, 24, 26, 28, 39, 42, 43] non-statistically significant associations were found for 26 exposures,[10, 14, 15, 18, 22-24, 32, 35, 41] while no associations were found for 13 agents.[13, 15, 22, 32, 35, 40, 41] Based on new studies, the level of evidence

remained unchanged for cleaning agents (i.e., moderate), but we specified that new subgroups with moderate evidence include chloramine and disinfection products.

Highly reactive chemicals: Six highly reactive chemicals were studied in five studies with low quality-rating.[13, 14, 18, 23, 24] For five groups of highly reactive chemicals, non-statistically significant associations were found,[14, 18, 23, 2413, 14, 18] while no statistically significant association was found for one group of reactive chemicals.[13] Based on new studies, we did not find evidence to change the level of evidence (i.e., limited/contradictory). Of note, Baur et. al. (2014)[6] rated persulfates as limited evidence, and we were not able, based on the resent literature, to upgrade this evaluation.

Unspecified group of other chemicals: Nine chemicals were studied in nine studies with low to high quality.[16, 17, 21, 23, 36-38, 42, 45] An association was found for all nine chemicals (i.e., 3-(Bromomethyl)-2-chloro-4-(methylsulfonyl)-benzoic acid, BCMBA, acrylates, alkyl-Cyanoacrylate, methyl-Cyanoacrylate, chlorhexidine, epoxy components (i.e., epoxy resin, polyamine hardener, triglycidyl iso-Cyanurate), potassium aluminium tetraflouride, polyvinyl Chloride (PVC)). The level of evidence for this broad group of other chemicals was upgraded to moderate, and we specifically upgraded acrylates to moderate evidence.

DISCUSSION

Main results

This systematic review included 37 studies of the relation between asthma and seven out of 10 selected potential occupational sensitizing exposures with no or limited evidence found in our overview of systematic review. No studies published since 2011 were found for amines, anhydrides, and molluscs. For the seven studied potential occupational sensitizing exposures, we upgraded main groups of crustaceans and enzymes to moderate evidence, and mammals, metals, and "mould, fungi and yeast" to

limited or contradictory evidence. For subgroups/specific exposures, pesticides, cleaning agents (i.e., chloramine and disinfection products), and an unspecified group of other chemicals (i.e., acrylates) were upgraded to moderate evidence.

Methodological considerations

The strengths of our systematic review were the comprehensive literature search strategy to identify all potentially relevant studies and the predefined study eligibility criteria to minimize bias arising from the selective consideration of evidence. Further strengths were the systematic approach to exclude studies, data extraction, and assessment of risk of bias performed by two reviewers in a transparent and replicable way. A potential limitation of the study was that the whole area of grey literature (e.g., reports or other not peer-reviewed literature) was not included. We expected that articles with high scientific quality and therefore the most informative studies to be published din peer review journals, and therefore we do not expect that the exclusion of grey literature have influenced our conclusions.

In earlier risk of bias tools and quality of evidence tools, case studies are regarded as low evidence, and they do not contain any relevant information with regards to the prevalence or incidence of health outcomes caused by occupational exposures. But particularly for asthma, case reports or case series with good quality specific inhalation challenges can be regarded as an experiment without significant confounder issues and with a high quality of both exposure and outcome data. Therefore, we developed a new tool in order to judge observational studies and case studies together as seen in appendix 4. The tool a priory did not give preferences to observational studies vs case or case series studies. We anticipate this tool to be useful in future reviews on studies dealing with risk factors for asthma.

Due to resource issues, we did not include all potential occupational sensitizing exposures with limited or no evidence from our overview. We used specific criteria for including 10 potential occupational sensitizing exposures, namely frequent potential occupational sensitizing exposures, suspected low molecular weight sensitizing exposures, and sensitizing exposures which are not considered well known causes of asthma. We prioritized frequently used exposures due the potential larger impact of preventive measures. We prioritized low molecular weight exposures due to the less well known mechanisms and diagnostic tools of those agents. Finally, we focused on exposures currently debated among clinicians and researchers, for example epoxy resins and pesticides.

We aimed to assess the evidence for potential occupational sensitizing exposures and asthma, and therefore we excluded studies on exposures known to be irritants without any suspicion of a specific immunological mechanism, e.g., chlorine and ammonia. On the other hand, we included main and subgroups/specific exposures in order to be as comprehensive as possible at the expense of also including non-sensitizing exposures. So even though the purpose was to review sensitizing exposures this review to some extend also deals with irritants without any specific mechanism of action. Also, some of the main groups (e.g., metal) included heterogeneous exposures (e.g., metal working fluids). We included these heterogeneous exposures in order to be as comprehensive as possible.

Discussion of results

The quality of the included studies was diverse ranging from low to high, but we were still able to upgrade the evidence level for more potential occupational sensitizing exposures, underlining the advantages of a systematic approach. New main groups with moderate evidence includes crustaceans and enzymes, while new subgroups/specific exposures with moderate evidence includes pesticides, chemicals/cleaning agents such as chloramine and disinfection products, and an unspecified group of other chemicals such as acrylates. The updated list now includes strong evidence of a relation for main

groups of wood dust, and moderate evidence for main groups of mites, fish, crustaceans, and enzymes. For subgroups/specific exposures, the updated list includes strong evidence for exposure to various laboratory animals, and moderate evidence for 60 subgroups/specific exposures. Case studies are still an important source of information and have added substantially to the evidence for several exposures.

At first sight, it is unexpected that the evidence for mammals was limited/contradictory. Due to high evidence in our overview for sensitizing exposures from cows and rats, they were not included in this review. Furthermore, sensitizing exposures well known to cause asthma for example from cats and dogs, are seldom investigated in occupational studies. So, the limited evidence reflects relatively few studies on more or less common mammals. Still it should be acknowledged, that numerous animal proteins have the capacity to cause IgE-mediated allergy and eventually to cause asthma.

The ambition of this review was in a transparent and systematic way to update the current evidence level for potential occupational sensitizing exposures using the results from a recent overview (Dalbøge et. al. *in draft*) as the point of departure. This resulted in an efficient although comprehensive evaluation of the existing literature. Baur´s et. al. (2014)[6] extensive systematic review was influential on the results in the overview. Of note, in this systematic review we did not use the same tool for evaluation risk of bias as Baur did; most importantly we gave more weight to high quality case studies. So we might have upgraded even more potential occupational sensitizing exposures if we have used our risk of bias tool on the several hundred studies included in the review by Baur et. al. (2014).[6] However, it was outside the scope of the current review to do this.

Conclusion

The systematic review provided an updated list of potential occupational sensitizing exposures able to cause asthma. New main groups with moderate evidence includes crustaceans and enzymes, while new subgroups/specific exposures with moderate evidence includes pesticides, chemicals/cleaning agents such as chloramine and disinfection products, and unspecified group of other chemicals such as acrylates. This updated list might help decision-making in occupational settings, and justification for further research.

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Contributors

AD and VS drafted the paper. The study methodology and results were discussed among all authors. All authors have reviewed the paper for important intellectual content, approved the final version of the manuscript, and take responsibility for the integrity of the work as a whole.

Competing interest

None

Table 2. Measure of association and conclusion of the 37 included studies

Allergens	Author	Design	Measure of association	95% CI	Conclusion	Risk of bias assessment	Initial level of evidence based on the overview	Current level of evidence based on the RCGP-system
Anhydrides (not Phthalic anhydride)							**Limited or contradictory evidence**	**Limited or contradictory evidence**
Amines							**No evidence**	**No evidence**
Biocides							**No evidence**	**No evidence**
Pesticides							(limited or contradictory)	(moderate)
Any pesticide use	Patel, 2018[30]	CS	POR=1.5	1.1-1.8	Statistically significant association for physician diagnosed current asthma; users vs. non-users	Low		
Glyphosate	Patel, 2018[30]	CS	POR=1.3	0.97-1.8	No statistically significant association for physician diagnosed current asthma	Low		
Herbicides	Patel, 2018[30]	CS	POR=1.3	1.0-1.8	The risk of physician diagnosed current asthma was significantly higher among users of herbicides vs. non-users	Low		
Insecticides	Patel, 2018[30]	CS	POR=2.0	1.2-3.3	Statistically significant association for physician diagnosed current asthma	Low		
Multiple pesticides	Liu, 2019[27]	CS	OR=1.24	1.03–1.49	Use of multiple pesticide associated with self-reported or clinically assessed asthma	Low		
Paraquat (1,1'-dimethyl-4,4' bipyridinium dichloride)	Cha, 2012[12]	CS	OR=2.18	0.99-4.82	The risks of self-reported physician-diagnosed asthma, was non-significantly increased among paraquat-applying farmers compared with non-paraquat-applying farmers	Low		
Phenoxy	Patel, 2018[30]	CS	POR=1.4	0.9-2.2	No statistically significant association for physician diagnosed current asthma	Low		
2,4-D	Patel, 2018[30]	CS	POR=1.3	0.8-2.1	No statistically significant association; physician diagnosed current asthma	Low		
Crustaceans (not lobsters, snow crabs)							**Limited or contradictory evidence**	**Moderate evidence**
Fish/shellfish	Beach, 2012[10]	CC	OR=2.06	1.26-3.49	Increased risk after Bayesian correction for exposure misclassification; Physician billing for asthma	Low		
Fish/shellfish	Ghosh, 2013[14]	Cohort	IPR=12.5	-	IPR estimated from available data; adult onset asthma with airflow limitation. No conclusion drawn.	Low		
Fish/shellfish	Hoy, 2013[18]	Cohort	OR=1.0	0.4-2.2	No statistically significant association for self-reported development of asthma after 13 years of age	Low		
Shellfish powder	Bertelsen, 2016[11]	Case-report	-	-	Shellfish powder can cause non-IgE mediated asthma	High		
Enzymes (not a-amylase from *Aspergillus oryzae*, detergent enzymes, Papain, Phytase from *Aspergillus niger*, various enzymes from *Bacillus subtilis* (alcalase, protease, maxatase, maxapem, esperase, cellulase, a-amylase, lipase, subtilisin)							**Limited or contradictory evidence**	**Moderate evidence**
Antigenic enzymes	Ghosh, 2013[14]	Cohort	OR=5.97	2.14-16.69	Statistical significant association for adult onset asthma with airflow limitation	Low		
Bacteral alpha-amylase termamyl	Baur, 2013[9]	Case-report	-	-	Bacteral alpha-Amylase termamyl caused asthma in one patient	Low		
Bioaerosol enzymes	Lillienberg, 2014[24]	Cohort	HR=1.3	0.6-3.1	No statistically significant association for new-onset asthma	Low		

Enzymes	Hoy, 2013[18]	Cohort	OR=2.2	0.3-16.0	No statistical significant association for development of self-reported asthma after 13 years of age	Low		
Enzymes	Dumas, 2014[13]	CS	OR=2.14	1.08-4.22	Statistically significant association for physician- diagnosed asthma	Low		
Savinase	Lipinska-Ojrzanowska, 2013[25]	Case-report	-	-	Savinase in dishwashing tablets caused asthma in one patient	High		
Mammals (not cows, rats)							**No evidence**	**Limited or contradictory evidence**
Animals (not specified)	Dumas, 2014[13]	CS	OR=1.62	1.00-2.60	Statistically significant association for physician- diagnosed asthma	Low		
Animal antigens	Ghosh, 2013[14]	Cohort	OR=1.48	0.55-4.01	No statistically significant association for adult onset asthma with airflow limitation	Low		
Animal antigens (HMW)	Beach, 2012[10]	CC	OR=2.42	1.45-4.30	Increased risk after Bayesian correction for exposure misclassification; Physician billing for asthma	Low		
Animal derived	Hoy, 2013[18]	Cohort	OR=1.0	0.5-1.9	No statistically significant association for development of self-reported asthma after 13 years of age	Low		
Lab animals	Simoneti, 2017[34]	CS				Moderate	(strong)	(strong)
		- Years (1.1-3.0) - Years (3.1-5.0) - Years (≥5.1)	PR=1.46 PR=3.29 PR=2.16	0.42-5.10 1.06-10.14 0.65-7.19	Workers exposed to lab animals from 3.1-5.0 years of exposure had increased risk of confirmed asthma compared to individuals exposed up to 1.0 year			
Mouse allergen (continuous)	Simoneti, 2016[33]	CS	RR=1.00	0.99-1.01	No association for BHR-confirmed asthma	High		
Rat or mouse antigens	Oppliger, 2017[29]	Cohort	-	-	Rat or mouse caused asthma in 6 persons	Moderate		
Raw pork meat	Jungewelter, 2019[20]	Case-report	-	-	One patient was diagnosed with occupational asthma from raw pork	Moderate		
Metals (not Platinum salts)							**No evidence**	**Limited or contradictory evidence**
Metal	Dumas, 2013[13]	CS	OR=0.51	0.22-1.16	No statistically significant association for physician- diagnosed asthma	Low		
Metal and metal fume	Beach, 2012[10]	CC	OR=1.82	1.34-2.66	Increased risk after Bayesian correction for exposure misclassification; Physician billing for asthma	Low		
Metal and metal fume antigens	Lillienberg, 2014[23]	Cohort	HR=1.3	0.6-2.6	No statistically significant association (note: same cohort as for Lillienberg, 2013 but with another JEM)	Moderate		
Metal and metal fume antigens	Ghosh, 2013[14]	Cohort	OR=2.13	1.05-4.32	Statistically significant association for adult onset asthma with airflow limitation	Low		
Metal sensitizers, fumes	Hoy, 2013[18]	Cohort	OR= 0.8	0.4-1.4	No statistically significant association for development of self-reported asthma after 13 years of age	Low		
Metal working fluids	Beach, 2012[10]	CC	OR=2.29	1.71-3.12	Increased risk after Bayesian correction for exposure misclassification; Physician billing for asthma	Low		
Metal working fluids	Ghosh, 2013[14]	Cohort	OR=1.03	0.54-1.97	No statistically significant association for self-reported physician-diagnosed adult onset asthma	Low		
Metal working fluids	Hoy, 2013[18]	Cohort	OR= 0.9	0.2-2.8	No statistically significant association for development of self-reported asthma after 13 years of age	Low		

Metal working fluids	Lillienberg, 2013[23]	Cohort	HR=0.9	0.3-2.6	No statistically significant association for new-onset asthma	Low		
Ba	Huang, 2016[19]	CC	OR=0.44	0.27-0.80	Statistical significant inverse association for self-reported asthma	Moderate		
Cd	Huang, 2016[19]	CC	OR=1.69	1.00-2.85	Statistical significant association for self-reported asthma	Moderate		
Cr	Huang, 2016[19]	CC	OR=4.89	3.04-7.89	Statistical significant association for self-reported asthma	Moderate		
Cu	Huang, 2016[19]	CC	OR=6.06	3.27-11.21	Statistical significant association for self-reported asthma	Moderate		
Fe	Huang, 2016[19]	CC	OR=0.41	0.26-0.64	Statistical significant inverse association for self-reported asthma	Moderate		
Mn	Huang, 2016[19]	CC	OR=0.23	0.14-0.39	Statistical significant inverse association for self-reported asthma	Moderate		
Mo	Huang, 2016[19]	CC	OR=3.76	2.30-6.16	Statistical significant association for self-reported asthma	Moderate		
Ni	Huang, 2016[19]	CC	OR=0.30	0.22-0.41	Statistical significant inverse association for self-reported asthma	Moderate		
Ni	Song, 2013[36]	Case-report	-	-	Nickel (and polyvinyl chloride) caused asthma in one patient	Moderate		
Pb	Huang, 2016[19]	CC	OR=0.48	0.29-0.80	Statistical significant inverse association for self-reported asthma	Moderate		
Rb	Huang, 2016[19]	CC	OR=0.07	0.03-0.15	Statistical significant inverse association for self-reported asthma	Moderate		
Se	Huang, 2016[19]	CC	OR=9.17	4.16-20.21	Statistical significant association for self-reported asthma	Moderate		
U	Huang, 2016[19]	CC	OR=6.99	4.37-11.19	Statistical significant association for self-reported asthma	Moderate		
Zn	Huang, 2016[19]	CC	OR=0.40	0.24-0.66	Statistical significant inverse association for self-reported asthma	Moderate		
Mould, fungi and yeast (not Aspergillus, Cladosporium, Penicllium)							**No evidence**	**Limited or contradictory evidence**
Alternaria alternata	Vincent, 2018[40]	CS	-	-	No association with severe asthma	Moderate		
Contact with mouldy documents	Roussel, 2012[32]	CS	OR=1.8	0.5–6.8	No statistically significant association for self-reported physician diagnosed asthma	Low		
Fungi in archives (>1 CFU/m^3)	Roussel, 2012[32]	CS	OR=0.8	0.3–2.4	No statistically significant association for self-reported physician diagnosed asthma	Low		
Fungi in archives (>170 CFU/m^3)	Roussel, 2012[32]	CS	OR=1.5	0.5-4.8	No statistically significant association for self-reported physician diagnosed asthma	Low		
Shitake mushrooms	Pravettoni, 2014[31]	Case-report	-	-	Shitake mushrooms induced asthma in one person	Low		
Molluscs							**Limited or contradictory evidence**	**Limited or contradictory evidence**
Other chemicals (not drugs, dyes, biocides, and isocyanates)							**Limited or contradictory evidence**	**Limited or contradictory evidence**

Cleaning agents							Moderate	Moderate
Alcohol degreaser	Walters, 2018[43]	Case-series	-	-	Alcohol degreaser caused asthma in one person	Low		
Ammonia	Vizcaya, 2013[41]		OR=2.7	0.9-8.2	No statistically significant association for clinically assessed asthma	Low		
Benzalkonium Chloride	Lipinska-Ojrzanowska, 2017[26]	Case-series	-	-	Benzalkonium chloride induced asthma in one case	Moderate		
Bleach	Vizcaya, 2013[41]	CC	OR=1.1	0.1-1.1	No statistically significant association for clinically assessed asthma	Low	(moderate)	(moderate)
Bleach/chlorine	Gonzalez, 2014[15]	CS	OR=1.01	0.47-2.18	No statistically significant association for physician-diagnosed asthma	Moderate		
Chloramine	Lipinska-Ojrzanowska, 2017[26]	Case-series	-	-	Chloramine induced asthma in two cases	Moderate		(moderate)
Chloramine: chlorine-releasing agents in combination with urine	Moore, 2017[28]	Case-series	-	-	Chlorine-releasing agents in combination with urine (chloramines) caused asthma in one case	Moderate		
Chloramine	Walters, 2018[43]	Case-series	-	-	Chloramine caused asthma in 25 persons	Low		
Cleaning agents (industrial)	Hoy, 2013[18]	Cohort	OR=1.1	0.8-1.7	No statistically significant association for development of self-reported asthma after 13 years of age	Low		(moderate)
Cleaning agents	Lillienberg, 2013[23]	Cohort	Men HR=2.6 Women=2.0	1.1-6.1 1.2-3.0	Statistically significant association for new-onset asthma Statistically significant association for new-onset asthma	Low		
Cleaning agents	Lillienberg, 2014[24]	Cohort	Men HR=2.3 Women=2.0	1.0-5.4 1.2-3.1	Statistically significant association; new onset asthma (note: same cohort as for Lillienberg, 2013[23] but with another JEM)	Low		
Cleaning agents	Weinmann, 2017[44]	Cohort	Low/med=1.55 High=2.79	0.51-4.71 1.14-6.83	Dose-dependent increase in incident asthma in relation to disinfectant	Low		
Cleaning agents (LMW)	Beach, 2012[10]	CC	OR=1.16	0.91-2.21	No statistical significant increased risk after Bayesian correction for exposure misclassification; Physician billing for asthma	Low		
Cleaning agents unspecified	Walters, 2018[43]	Case-series	-	-	Chloramine caused asthma in 10 persons	Low		
Cleaning products (dilation, task)	Gonzalez, 2014[15]	CS	OR=0.81	0.39-1.65	No statistically significant association for physician-diagnosed asthma	Moderate		
Cleaning (essential tasks)	Le Moual, 2013[22]	CS	OR=1.42	0.92-2.20	No statistically significant association current asthma	Low		
Cleaning (general task)	Gonzalez, 2014[15]	CS	OR=2.26	0.95-5.35	No statistically significant association for physician-diagnosed asthma	Moderate		
Chemical products (cleaning)	Le Moual, 2013[22]	CS	OR=0.97	0.54-1.30	No statistically significant association for current asthma	Low		
Degreasers	Vizcaya, 2013[41]	CC	OR=1.2	0.5-3.0	No statistically significant association for clinically assessed asthma	Low		
Denatonium	Walters, 2018[43]	Case series	-	-	Denatonium caused asthma in one person	Low		
Disinfection (dilution, task)	Gonzalez, 2014[15]	CS	OR=4.01	1.34-12.00	Statistically significant association for physician-diagnosed asthma	Moderate		(moderate)
Disinfecting products	Ghosh, 2013[14]	Cohort	OR=1.91	1.03-3.56	Statistically significant association for adult onset asthma with airflow limitation	Low		
Disinfection products/cleaning	Dumas, 2014[13]	CS	OR=1.02	0.52-2.01	No association with asthma	Low		
Disinfection task	Gonzalez,	CS	OR=3.16	1.17-8.52	Statistically significant association for physician-diagnosed asthma	Moderate		

(general task)	2014[15]							
Domestic wizard	Le Moual, 2013[22]	CS	OR=0.61	0.39-0.97	Statistically significant inverse association for self-reported current asthma	Low		
Drain products	Vizcaya, 2013[41]	CC	OR=0.2	0.0-2.9	No statistically significant association for clinically assessed asthma	Low		
Dust mop products	Vizcaya, 2013[41]	CC	OR=1.9	0.7-5.2	No statistically significant association for clinically assessed asthma	Low		
EDTA	Walters, 2018[43]	Case series	-	-	EDTA caused asthma in one person	Low		
Ethanolamine containing compounds	Vandenplas 2013[39]	Case series	-	-	An association was found in two persons	High		
Ethylene diamine	Walters, 2018[43]	Case series	-	-	Ethylene diamine caused asthma in one person	Low		
Formadelhyde	Lipinska-Ojrzanowska, 2017[26]	Case-series	-	-	Formadelhyde induced asthma in one case	Moderate	(moderate)	(moderate)
Glass cleaners	Vizcaya, 2013[41]	CC	OR=1.0	0.3-2.7	No statistically significant association for clinically assessed asthma	Low		
Glutaraldehyde	Lipinska-Ojrzanowska, 2017	Case-series	-	-	Glutaraldehyde induced asthma in one case	Moderate	(moderate)	(moderate)
Glutaraldehyde	Walters, 2018[43]	Case series	-	-	Glutaraldehyde caused asthma in 21 persons	Low		
Gluteraldehyde containing compounds	Vandenplas 2013[39]	Case series	-	-	An association was found in three persons	High		
Home cleaning (>1 day/week)	Le Moual, 2013[22]	CS	OR=1.34	0.87-2.05	No statistically significant association between current asthma	Low		
Hydrochloric acid	Vizcaya, 2013[41]	CC	OR=1.5	0.3-7.7	No statistically significant association for clinically assessed asthma	Low		
Isothiazolinone	Walters, 2018[43]	Case-series	-	-	Isothiazolinone caused asthma in three persons	Low		
Latex	Beach, 2012[10]	Cohort	OR=1.79	1.27-2.53	Statistically significant association; Physician billing for asthma	Low		
Latex	Hoy, 2013[18]	Cohort				Low		
		- Yes vs no	OR=1.40	0.9-2.3	No statistically significant association for self-reported development of asthma after 13 years of age			
		- Ref	OR=1.00					
		- 1-5 years	OR=0.72					
		- 6-15 years	OR=1.61					
		- 16 years	OR=2.65					
Latex	Lillienberg, 2013[23]	Cohort	Men HR=1.7	0.7-4.2	No statistically significant association for new-onset asthma for both men and women	Low		
			Women HR= 1.3	0.8-2.3				
Latex	Lillienberg, 2014	Cohort	HR men=1.4	0.4-4.4	No statistically significant association for new-onset asthma for both men and women (Note: Same cohort as Lillienberg, 2013[23] but with another JEM)	Low		
			Women=1.3	0.9-1.8				
Latex	Lipinska-Ojrzanowska, 2017	Case-series	-	-	Latex induced asthma in three cases	Moderate		
Latex	Singh, 2013[35]	CS			No statistically significant association for atopic and non-atopic asthma	Low		
		- Atopic	OR=0.72	0.32-1.60				
		- Non-atopic	OR=0.78	0.31-1.96				
Latex antigens	Ghosh, 2013[14]		OR=1.23	0.67-2.26	No statistically significant association for adult onset asthma with airflow limitation	Low		
Latex gloves	Gonzalez,	CS	OR=0.69	0.32-1.51	No statistically significant association for physician-diagnosed	Moderate		

	2014[15]				asthma			
Limescale removers	Vizcaya, 2013[41]	CC	OR=0.2	0.1-0.7	No statistically significant association for clinically assessed asthma	Low		
Multi-use products	Vizcaya, 2013[41]	CC	OR=2.3	0.7-7.0	No statistically significant association for clinically assessed asthma	Low		
Peracetic acid	Walters, 2018[43]	Case-series	-	-	Peracetic acid caused asthma in two persons	Low		
Polishes and waxes	Vizcaya, 2013[41]	CC	OR=1.1	0.2-5.1	No statistically significant association for clinically assessed asthma	Low		
Triclosan	Walters, 2018[43]	Case-series	-	-	Triclosan caused asthma in one person	Low		
Soaking solutions preparation (task)	Gonzalez, 2014[15]	CS	OR=1.56	0.77-3.18	No statistically significant association; physician-diagnosed asthma	Moderate		
Sodium hydroxide	Walters, 2018[43]	Case series	-	-	Sodium hydroxide caused asthma	Low		
Spray, mist or steam	Singh, 2013[35]	CS					(moderate)	(moderate)
		- Atopic	OR=5.11	0.52-50.23	No statistically significant association for both atopic and non-atopic asthma	Low		
		- Non-atopic	OR=9.57	0.21-42.6				
Spray or aerosol form: Multi-use products	Vizcaya, 2013[41]	CC	OR=4.1	1.0-18.0	Statistically significant association for clinical assessed asthma	Low		
Spray or aerosol form: Degreasers	Vizcaya, 2013[41]	CC	OR=1.1	0.4-3.1	No statistically significant association for clinical assessed asthma	Low		
Spray or aerosol form: Dust mop products	Vizcaya, 2013[41]	CC	OR=1.5	0.6-3.9	No statistically significant association for clinical assessed asthma	Low		
Spray or aerosol form: Limescale removers	Vizcaya, 2013[41]	CC	OR=1.5	0.5-5.0	No statistically significant association for clinical assessed asthma	Low		
Spray or aerosol form: Glass cleaners	Vizcaya, 2013[41]	CC	OR=1.2	0.3-5.9	No statistically significant association for clinical assessed asthma	Low		
Number of different sprays	Vizcaya, 2013[41]	CC						
		- 0	OR=1.0	-	No statistically significant association for clinical assessed asthma	Low		
		- 1-2	OR=0.8	0.3-2.4				
		- 3-5	OR=2.1	0.6-7.4				
Spray use	Weinmann, 2017[44]	Cohort	OR: Low=0.70	0.23-2.06	Weak indication of a dose-dependent increase in incident asthma in relation to spray use	Low		
			Medium=0.78	0.26-2.36				
			High=2.79	0.84-9.20				
Spray use at work (task)	Gonzalez, 2014[15]	CS	OR=0.84	0.42-1.69	No statistically significant association for physician-diagnosed asthma	Moderate		
Spray use (1 type)	Le Moual, 2013[22]	CS	OR=0.68	0.44-1.04	No statistically significant association for current asthma	Low		
Spray use (2 types)	Le Moual, 2013[22]	CS	OR=1.67	1.08-2.56	Statistically significant association for current asthma	Low		
Soaps or detergents	Vizcaya, 2013[41]	CC	OR=0.2	0.1-0.7	Soap and detergents showed a statistically significant inverse association with clinically assessed asthma	Low		
Sodium hydroxide	Walters, 2018[43]	Case-series	-	-	Sodium hydroxide caused asthma in one person	Low		
Stain removers	Vizcaya, 2013[41]	CC	OR=0.8	0.1-4.1	No statistically significant association for clinically assessed asthma	Low		
Quaternary ammonia compounds (QAC)	Vandenplas 2013[39]	Case series	-	-	An association was found in 10 persons	High	(moderate)	(moderate)
QAC	Gonzales, 2014[15]	CS	OR=7.56	1.84-31.05	Statistically significant association for physician-diagnosed asthma	Moderate		
QAC and glutaraldehyde	Vandenplas 2013[39]	Case series	-	-	An association was found in one persons	High		

QAC	Walters, 2018[43]	Case-series	-	-	Quaternary ammonium compounds caused asthma in nine persons	Low		
Highly reactive chemicals							Limited or contradictory evidence	Limited or contradictory evidence
Highly reactive chemicals	Hoy, 2013[18]	Cohort	OR=1.2	0.7-2.0	No statistically significant association for development of self-reported asthma after 13 years of age	Low		
Highly reactive chemicals	Ghosh, 2013[14]	Cohort	OR=1.23	0.61-4.28	No statistically significant association for adult onset asthma with airflow limitation	Low		
Highly reactive chemicals	Dumas, 2014[13]	CS	OR=0.97	0.61-1.53	No statistically significant association for physician- diagnosed asthma	Low		
Reactive chemical	Lillienberg, 2013[23]	Cohort	Men HR=1.0 Women=1.6	0.3-3.1 0.8-3.0	No statistically significant association for new-onset asthma No statistically significant association for new-onset asthma	Low		
Highly reactive chemicals	Lillienberg, 2014[24]	Cohort	Men HR=2.1 Women=1.4	0.99-4.30 0.96-2.00	No statistically association for new-onset asthma (note: same cohort as for Lillienberg, 2013[23] but with another JEM)	Low		
Reactive chemicals-isocyanates	Ghosh, 2013[14]	Cohort	OR=1.91	0.63-5.79	No statistically significant association for adult onset asthma with airflow limitation	Low		
Unspecified group of other chemicals							Limited or contradictory evidence	Moderate evidence
3-(Bromomethyl)-2-chloro-4-(methylsulfonyl)-benzoic acid, BCMBA	Suojalehto, 2018[37]	Case series	-	-	An association between 3-(Bromomethyl)-2-chloro-4-(methylsulfonyl)-benzoic and asthma was found	High		
Acrylates	Lillienberg, 2013[23]	Cohort	HR=1.8	0.8-3.7	No statistically significant association for new-onset asthma	Low		(moderate)
Acrylates	Walters, 2017[42]	Case-series	-	-	Acrylates caused asthma in two patients	Low		
Acrylic polymers	Walters, 2017[42]	Case-series	-	-	Acrylic polymers caused asthma in two patients	Low		
Cyanoacrylates including alkyl-cyanoacrylates	Walters, 2017[42]	Case-series	-	-	Cyanoacrylates caused asthma in eight patients	Low		
Methyl methacrylates	Walters, 2017[42]	Case-series	-	-	Methyl methacrylates caused asthma in eight patients	Low		
Chlorhexidine	Wittczak, 2013[45]	Case-series	-	-	Chlorhexidine caused asthma in two patients	High		
Epoxy	Lillienberg, 2013[23]	Cohort	HR=2.4	1.3-4.5	Statistically significant association for new-onset asthma	Low		
Epoxy components: epoxy resin	Suojalehto, 2019[38]	Case-series	-	-	Epoxy resin caused sensitizer-induced occupational asthma in some exposed cases	Moderate		
Epoxy components: triglycidyl iso-cyanurate	Suojalehto, 2019[38]	Case-series	-	-	Triglycidyl isocyanurate caused sensitizer-induced occupational asthma in some exposed cases	Moderate		
Hair dyes e.g., persulfates,	Helaskoski, 2014[16]	Case-series	-	-	Association found in 5 cases	Moderate		

permanent wave solutions, hair bleach						
Potassium aluminium tetrafluoride	Lastovkova, 2015[21]	Case-series	-	-	4 of 5 patients had occupational asthma based	Moderate
Polyvinyl Chloride (PVC)	Song, 2013[36]	Case-report	-	-	Polyvinyl chloride (and nickel) caused asthma in one patient	Moderate
Persulfate salts (hair-bleaching products)	Hougaard, 2012[17]	Case-report	-	-	An association between persulfate salts and asthma was found in 1 case	Low

BHR; Bronchial hyperresponsiveness, CC; Case-control study, CS: Cross-sectional study, vs; versus, OR; Odds ratio, POR; Prevalence odds ratio

APPENDICES

Appendix 1: PECO for peer-reviewed studies

Population

Adult human population in or above working age

Exposure

Exposure definition: Primary exposures included potential occupational sensitizing exposures suspected to cause asthma. The sensitizing exposures included both high- and certain low-molecular-weight agents, which were divided into the following groups;

- Amines
- Anhydrides (not Phthalic anhydride)
- Biocides
- Crustaceans (not lobsters and snow crabs)
- Enzymes (not a-amylase from *Aspergillus oryzae*, detergent enzymes, Papain, Phytase from *Aspergillus niger*, various enzymes from *Bacillus subtilis* (alcalase, protease, maxatase, maxapem, esperase, cellulase, a-amylase, lipase, subtilisin)
- Mammals (not cows, rats)
- Metals (not Platinum salts)
- Mould, fungi and yeast (not Aspergillus, Cladosporium, Penicllium)
- Molluscs
- Other chemicals (not drugs, dyes, biocides, and isocyanates)

Exposure assessment: We included studies with exposure information based on subjective (self-reports) or objective (e.g., expert based, observations, technical measurements) assessment, and where exposure estimates were quantified ranging from dichotomous to continuous variables.

Studies with more proxy measure of exposures such as job title or industry (no exposure quantification) was not included.

Comparison

We included studies with exposure contrast between persons/groups (e.g., exposed vs. non/low exposed). Only studies, where a measure of association of the effect of sensitizing exposures on asthma has been estimated or is possible to estimate was included.

Outcome

Outcome definition: Outcome was defined as asthma. Asthma is considered a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper-responsiveness, and an underlying inflammation. Outcome did not include pre-existing asthma aggravated by work (might be difficult to evaluate).

Outcome assessment:

In observational studies, we included studies, where outcome was assessed as:

- Self-reported by workers, or
- Clinical diagnosis as reported by workers, or
- Clinical diagnosis by medical expert, or

Objective measurements: spirometry (LFT, sPET), immunology (as marker of effect), and provocation (lung) as the latter verification by experimental condition will be more specific. In case-reports, we included studies where exposure information is based on self-reported symptoms in combination with objective measurements (e.g., spirometry (LFT, sPET), immunology (as marker of effect), or provocation (skin, lung)).

Appendix 2: Full search string for literature search in PudMed/MEDLINE

((((((((((((((((((((((((((((signs and symptoms, respiratory[MeSH Terms]))) OR ((allergy and immunology[MeSH Terms]))) OR allergy[Text Word]) OR immunology[Text Word]) OR "respiratory function tests"[MeSH Terms]) OR respiratory function test*[Text Word]) OR pulmonary function test*[Text Word]) OR lung function test*[Text Word]) OR bronchial hyperreactivity[MeSH Terms]) OR bronchial hyperreactivit*[Text Word]) OR airway obstruction[MeSH Terms]) OR airway obstruction[Text Word]) OR respiratory hypersensitivity[MeSH Terms]) OR airway hyper responsiveness[Text Word]) OR respiratory hyper responsiveness[Text Word]) OR respiratory hypersensitivit*[Text Word]) OR lung diseases, obstructive[MeSH Terms]) OR obstructive lung disease*[Text Word]) OR obstructive pulmonary disease*[Text Word]) OR asthma[MeSH Terms]) OR asthma, occupational[MeSH Terms]) OR occupational asthma*[Text Word])) **AND** ((((((((((((workplace[MeSH Terms]) OR occupational exposure[MeSH Terms]) OR occupational diseases[MeSH Terms]) OR occupational exposure*[Text Word]) OR work related[Text Word]) OR workplace*[Text Word]) OR work environment[Text Word]) OR job site*[Text Word]) OR work location*[Text Word]) OR work site*[Text Word]) OR work place*[Text Word]) OR occupation[Text Word]) OR work[MeSH Terms])) **AND** ((((((((((((((((((allergens[MeSH Terms]) OR allergic[Text Word]) OR allergen*[Text Word]) OR antigen*[Text Word]) OR antigens[MeSH Terms]) OR hypersensitivit*[Text Word]) OR immediate[Text Word]) OR ige[Text Word]) OR immunoglobulin e[Text Word]) OR sensation[MeSH Terms]) OR hypersensitivity, immediate[MeSH Terms]) OR ((bites and stings[MeSH Terms]))) OR fungi[MeSH Terms]) OR dust[MeSH Terms]) OR feathers[MeSH Terms]) OR sensitization[Text Word]) OR sensitisation[Text Word]) OR asthmogen*[Text Word]) OR asthmagen*[Text Word])) **AND** ((((((((((((((((causality[MeSH Terms]) OR etiology[MeSH Terms]) OR risk factors[MeSH

Terms]) OR etiology[MeSH Subheading]) OR causation[Text Word]) OR causing[Text Word]) OR causalit*[Text Word]) OR etiolog*[Text Word]) OR epidemiolog*[Text Word]) OR reinforcing factor*[Text Word]) OR enabling factor*[Text Word]) OR predisposing factor*[Text Word]) OR odds ratio[MeSH Terms]) OR odds ratio*[Text Word]) OR risk[MeSH Terms]) OR incidence proportion rate*[Text Word]) OR incidence[MeSH Terms]) OR incidence rate*[Text Word]))) NOT ((animals[MeSH Terms]) NOT humans[MeSH Terms]))) **AND** ((danish[Language]) OR english[Language])

Appendix 3: Study exclusion criteria

1) The following exclusion criteria were used at title/abstract screening:

- No indication of asthma or "unspecific lung diseases" as outcome measure, or
- No indication of occupational allergens as exposure, or
- No indication of evaluation of association between asthma and occupational allergens, or
- Other reasons:
    - Animal study, children/student study, or
    - A systematic review; abstract should indicate that the literature search was performed systematic
    - Not English/Danish language
    - Books, letters to editor, reviews, abstracts only will be excluded

2) The following exclusion criteria were used at full paper reading:

- Study outcome does not fulfill outcome definition (i.e. outcome definition in PECO), or
- Study exposures does not fulfill exposure definition (i.e. exposure definition in PECO), or
- No indication of evaluation of association between asthma and occupational allergens, or
- Other reasons
    - Animal study, children/student study, or
    - A systematic review; no indication of a systematic literature search
    - Not English/Danish language
    - Books, letters to editor, reviews, abstracts only will be excluded

Appendix 4: Risk of bias assessment including 10 items. Item 1-9 was scored "High" or "Low", while item 10 could be scored "High", "Moderate", Low" or "Critically low".

Item		Objective	Scoring	Comment
1	Study design	Basic principle for causal inference	• Experimental: 1 • Observational: 0	• Experimental studies with specific inhalation challenge (SIC) of individual participants or intervention studies=1 • Other epidemiological studies=0
2	Population	Asses risk factors of incident asthma	• Population at risk: 1 • Patients: 0	• Epidemiological studies of incident asthma=1 • Other types of studies: SIC in case reports will by definition only include prevalent asthma=0
3	Participation rate	Assess potential for selection bias	• High: 1 • Low: 0	• ≥60%=1 • <60%, unknown or case-reports=0
Exposure				
4	Exposure specificity	Assess specific exposure	• High: 1 • Low: 0	• Specific allergens, chemicals, plants, animals =1 • Task, product, process, occupation, industry=0
5	Exposure assessment - I	Assess potential for information bias	• Blinded/objective: 1 • Not blinded/ subjective: 0	• Blinded SIC with relevant sham=1 • SIC with no sham=0 • Observational study with independent exposure assessment=1 • Self-reported exposure=0
6	Exposure assessment - II	Individual or group-based assessment	• Individual assessment:1 • Group-based assessment: 0	• Self-reports, measurements on the individual level, employment records=1 • JEMs or other group-based approaches=0
Outcome				
7	Outcome assessment	Assess potential for information bias	• Clinical: 1 • Other: 0	• Objective measurements of variability of lung function (e.g. reversibility, bronchial hyperreactivity or peak flow)=1 • Other=0
Association				
8	Confounders adjusted for	Assess potential for confounding	• Appropriate: 1 • Inappropriate: 0	• Observational studies: smoking, age, BMI and atopy (adjustment or stratification), case-reports with SIC if sham=1 (own control) • Other=0
9	Exposure-response relation	Core criterion for causality	• Assessed: 1 • Not assessed: 0	• At least 3 levels of exposure or continuous exposure metric=1 • Other=0

Item 10: Rating overall confidence in the results of the study

HIGH - Zero or one non-critical weakness:
The study provides an accurate estimate of the association between exposure and outcome.

MODRATE - More than one non-critical weakness*:
The study has more than one weakness, but no critical flaws. It may provide an accurate estimate of the association between exposure and outcome.

LOW - One critical flaw with or without non-critical weaknesses:
The study has a critical flaw and may not provide an accurate estimate of the association between exposure and outcome

CRITICALLY LOW - More than one critical flaw with or without non-critical weaknesses:
The study has more than one critical flaw and should not be relied on to provide an accurate estimate of the association between exposure and outcome

***Note:** Multiple non-critical weaknesses may diminish confidence in the study and it may be appropriate to move the overall appraisal down from moderate to low confidence

Appendix 5. Modification of the Royal College of General Practioners three star system (RCGP)[6]

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, or 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, or 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 evidence	Based on clinical studies, theoretical considerations and/or clinical consensus

Appendix 6: List of 98 excluded studies and the reason for exclusion

Excluded studies	Reason for exclusion
Anderson, Naomi J.; Reeb-Whitaker, Carolyn K.; Bonauto, David K.; Rauser, Edmund. Work-Related Asthma in Washington State Journal of Asthma 2011;48(8):773-782	Study outcome does not fulfil outcome definition
Ayaaba E.; Li Y.; Yuan J.; Ni C. Occupational respiratory diseases of miners from two gold mines in Ghana. International Journal of Environmental Research and Public Health / 2017;14(3):337	Study outcome does not fulfil outcome definition
Balbay, Ege Gulec; Toru, Umran; Arbak, Peri; Balbay, Oner; Suner, Kezban Ozmen; Annakkaya, Ali Nihat. Respiratory symptoms and pulmonary function tests in security and safety products plant workers. International Journal of Clinical and Experimental Medicine 2014;7(7):1883-1886	Study outcome does not fulfil outcome definition
Baldi, Isabelle; Robert, Celine; Piantoni, Florence; Tual, Severine; Bouvier, Ghislaine; Lebailly, Pierre; Raherison, Chantal. Agricultural exposure and asthma risk in the AGRICAN French cohort. International journal of hygiene and environmental health 2014;217(4-5):435-442	Study exposures does not fulfil exposure definition
Cauz, Paola; Bovenzi, M.; Filon, Francesca Larese. Laboratory animal allergy: follow-up in a research centre. Medicina Del Lavoro 2014;105(1):30-36	Other reasons (e.g. abstract only, review)
Chatti, S.; Maoua, M.; Rhif, H.; Dahmoul, M.; Abbassi, A.; Mlaouah, A. J.; Salah, H. Hadj; Debbabi, F.; Mrizak, N. Occupational asthma in the Tunisian central region: Etiologies and professional status. Revue de pneumologie clinique 2011;67(5):281-288	Other reasons (e.g. abstract only, review)
De Olim C.; Begin D.; Boulet L.-P.; Cartier A.; Gerin M.; Lemiere C. Investigation of occupational asthma: Do clinicians fail to identify relevant occupational exposures? Canadian Respiratory Journal / 2015;22(6):341-347	No evaluation of the association between occupational allergens and asthma
Dumas, Orianne; Le Moual, Nicole; Siroux, Valerie; Heederik, Dick; Garcia-Aymerich, Judith; Varraso, Raphaelle; Kauffmann, Francine; Basagana, Xavier. Work related asthma. A causal analysis controlling the healthy worker effect. Occupational and environmental medicine 2013;70(9):603-610	Study outcome does not fulfil outcome definition
Feary, Johanna; Fitzgerald, Bernadette; Schofield, Susie; Jones, Meinir; Cullinan, Paul. Sensitisation to mouse allergens in contemporary laboratory animal workers: The SPIRAL study. European Respiratory Journal 2016;48(Journal Article)	Other reasons (e.g. abstract only, review)
Ferraz E.; Simoneti C.S.; Rodrigues M.; Freitas A.S.; Arruda L.K.; Bagatin E.; Vianna E.O. Association of dust allergen in animal	Other reasons (e.g. abstract

laboratories and atopic sensitization . American Journal of Respiratory and Critical Care Medicine 2015;191(Meeting Abstracts)	only, review)
Francuz, B.; Demange, V.; Mousel, M. -L; Grzebyk, M.; Nicaise, P.; Chollet-Martin, S.; Choudat, D. Allergic or irritative symptoms in preparation laboratory and animal facilities personnel in a research institute. Archives Des Maladies Professionnelles Et De L Environnement 2014;75(2):126-134	Other reasons (e.g. abstract only, review)
Galli, Luigina; Facchetti, Susanna; Raffetti, Elena; Donato, Francesco; D'Anna, Mauro. Respiratory diseases and allergic sensitization in swine breeders: a population-based cross-sectional study. Annals of Allergy Asthma & Immunology 2015;115(5):402-407	Study outcome does not fulfil outcome definition
Graff, Pal; Bryngelsson, Ing-Liss; Fredrikson, Mats; Flodin, Ulf. Adult onset asthma in non-allergic women working in dampness damaged buildings: A retrospective cohort study. American Journal of Industrial Medicine 2019;62(4):357-363	Study exposures does not fulfil exposure definition
Guarnieri G.; Cattoni I.; Barbetta G.; Liviero F.; Mason P.; Scarpa M.C.; Maestrelli P. Features of occupational asthma in Northern Italy from 1987 to 2012. European Respiratory Journal / 2013;42(SUPPL. 57)	Other reasons (e.g. abstract only, review)
Harris-Roberts J.; Robinson E.; Fishwick D.; Fourie A.; Rees D.; Spies A.; Curran A.; Sen D.; Barber C. Sensitization and symptoms associated with soybean exposure in processing plants in South Africa. American Journal of Industrial Medicine / 2012;55(5):458-464	Study exposures does not fulfil exposure definition
Hawley, Brie; Cummings, Kristin J.; Mohammed, Mohammed; Dimmock, Anne E.; Bascom, Rebecca. Allergic sinusitis and severe asthma caused by occupational exposure to locust bean gum: Case report. American Journal of Industrial Medicine 2017;60(7):658-663	Study exposures does not fulfil exposure definition
Henneberger P.; Liang X.; Lillienberg L.; Dahlman-Hoglund A.; Toren K.; Andersson E. Association of asthma exacerbation with objective and subjective assessments of occupational exposure. European Respiratory Journal / 2014;44(SUPPL. 58)	Other reasons (e.g. abstract only, review)
Jaiyesimi A.; Agbaje S. Respiratory symptoms and lung function indices of poultry workers and age-matched apparently healthy individuals in Ibadan, Nigeria. Physiotherapy (United Kingdom) / 2015;101(SUPPL. 1):eS667-eS668	Other reasons (e.g. abstract only, review)
Jones, M.; Welch, J.; Turvey, J.; Cannon, J.; Clark, P.; Szram, J.; Cullinan, P. Prevalence of sensitization to 'improver' enzymes in UK supermarket bakers. Allergy 2016;71(7):997-1000	Study outcome does not fulfil outcome definition
Kim D.; Kim B.; Lee K.; Shin J. A case of occupational asthma occurred in the subway maintenance worker. European Respiratory Journal / 2015;46(SUPPL. 59)	Other reasons (e.g. abstract only, review)
Kwon S.-C.; Song J.; Kim Y.-K.; Calvert G.M. Work-related asthma in Korea - findings from the Korea Work-Related Asthma Surveillance	No evaluation of the association

(KOWAS) program, 2004-2009. Allergy, Asthma and Immunology Research / 2014;7(1):51-59	between occupational allergens and asthma
Laborde-Casterot, Herve; Rosenberg, Nicole; Dupont, Patricia; Garnier, Robert. Is the Incidence of Aliphatic Amine-Induced Occupational Rhinitis and Asthma Underestimated? American Journal of Industrial Medicine 2014;57(12):1303-1310	Study outcome does not fulfil outcome definition
Laborde-Casterot, Herve; Villa, Antoine F.; Rosenberg, Nicole; Dupont, Patricia; Lee, Hwee Min; Garnier, Robert. Occupational rhinitis and asthma due to EDTA-containing detergents or disinfectants. American Journal of Industrial Medicine 2012;55(8):677-682	Study outcome does not fulfil outcome definition
Laszlo, Endre. Occupational asthma in Hungary. Orvosi hetilap 2015;156(19):769-778	Other reasons (e.g. abstract only, review)
Le Moual N.; Bedard; Dumas; Varraso; Kauffmann; Zock. Relevance of exposure to cleaning agents beyond cleaning professionals: Private homes and healthcare workers. Occupational and Environmental Medicine / 2013;70(SUPPL. 1)	Other reasons (e.g. abstract only, review)
Liccardi, Gennaro; Emenius, Gunnel; Merritt, Anne-Sophie; Salzillo, Antonello; D'Amato, Maria; D'Amato, Gennaro. Direct and Indirect Exposure to Horse: Risk for Sensitization and Asthma. Current Allergy and Asthma Reports 2012;12(5):429-437	Study outcome does not fulfil outcome definition
Lipinska-Ojrzanowska A.A.; Wiszniewska M.; Nowakowska-Swirta E.; Walusiak-Skorupa J.M. Airways inflammation in work-related asthma due to high and low molecular weight agents. Allergy: European Journal of Allergy and Clinical Immunology / 2017;72(Supplement 103):240-241	Other reasons (e.g. abstract only, review)
Lipinska-Ojrzanowska A.; Wiszniewska M.; Walusiak-Skorupa J. Work-related asthma in cleaners. Allergy: European Journal of Allergy and Clinical Immunology / 2014;69(SUPPL. 99):116	Other reasons (e.g. abstract only, review)
Lipinska-Ojrzanowska, Agnieszka; Wiszniewska, Marta; Swierczynska-Machura, Dominika; Wittczak, Tomasz; Nowakowska-Swirta, Ewa; Palczynski, Cezary; Walusiak-Skorupa, Jolanta. Work-related respiratory symptoms among health centres cleaners: A cross-sectional study. International journal of occupational medicine and environmental health 2014;27(3):460-466	Study outcome does not fulfil outcome definition
Malo, J. -L; Ghezzo, H.; L'Archeveque, J. Distinct temporal patterns of immediate asthmatic reactions due to high- and low-molecular-weight agents. Clinical and Experimental Allergy 2012;42(7):1021-1027	Study outcome does not fulfil outcome definition
Marchetti N.; Garshick E.; Kinney G.L.; McKenzie A.; Stinson D.; Lutz S.M.; Criner G.J. Risk of moderate to severe COPD and chronic respiratory symptoms attributable to occupational exposure is similar for men and women in COPDgene. American Journal of Respiratory and	Other reasons (e.g. abstract only, review)

Critical Care Medicine / 2013;187(MeetingAbstracts)	
Mazurek J.M.; White G.E.; Rodman C.; Schleiff P.L. Farm work-related asthma among US primary farm operators. Journal of agromedicine / 2015;20(1):31-42	Study exposures does not fulfil exposure definition
Meza, Francisco; Chen, Lilia; Hudson, Naomi. Investigation of Respiratory and Dermal Symptoms Associated With Metal Working Fluids at an Aircraft Engine Manufacturing Facility. American Journal of Industrial Medicine 2013;56(12):1394-1401	Study outcome does not fulfil outcome definition
Mezni, A. Benzarti; Babay, S.; Ben Jemaa, A. Occupational asthma to the pyrolysis products of plastics in a company manufacturing protective respiratory masks. About 2 cases. Revue Francaise D Allergologie 2012;52(7):474-479	Other reasons (e.g. abstract only, review)
Mezni, A. Benzarti; Guissi, R.; Hsinet, J.; Ben Maiz, N.; Essid, D.; Hamdouni, M.; Ben Jemaa, A. Analysis of acknowledged occupational asthma records over a period of 15 years in a population in northern Tunisia. Revue Francaise D Allergologie 2018;58(6):427-436	Other reasons (e.g. abstract only, review)
Minov J.; Karadzinska-Bislimovska J.; Stoleski S.; Mijakoski D.; Atanasovska A. Distribution of sensitizer-induced occupational asthma in R. Macedonia by occupation in the period 2005-2017. European Respiratory Journal / 2018;52(Supplement 62)	Other reasons (e.g. abstract only, review)
Moghtaderi, M.; Farjadian, S.; Hasiri, M. Abbaszadeh. Animal allergen sensitization in veterinarians and laboratory animal workers. Occupational Medicine-Oxford 2014;64(7):516-520	Study outcome does not fulfil outcome definition
Moghtaderi, Mozhgan; Farjadian, Shirin; Hosseini, Zeynab; Raayat, Alireza. Increased Risk of Horse Sensitization in Southwestern Iranian Horse Riders. International journal of occupational medicine and environmental health 2015;28(5):909-913	Study outcome does not fulfil outcome definition
Money A.; Carder M.; Hayes J.P.; Noone P.; Bourke P.; Hayes J.; Agius R. Work related respiratory ill health (WRRIH): Republic of Ireland, Northern Ireland, Great Britain 2005-2012. Irish Journal of Medical Science / 2014;183(11 SUPPL. 1):S497	Other reasons (e.g. abstract only, review)
Munoz X.; Meca O.; Sanchez-Ortiz M.; Olle-Monge M.; Morell F.; Cruz M.-J. Specific inhalation challenge in occupational asthma: Differences in response depending on the type of agent. American Journal of Respiratory and Critical Care Medicine / 2013;187 (MeetingAbstracts)	Other reasons (e.g. abstract only, review)
Mwanga H.H.; Baatjies R.; Singh T.; Jeebhay M. Risk factors for work-related asthma in health care workers with exposure to diverse cleaning agents. Allergy: European Journal of Allergy and Clinical Immunology / 2016;71(Supplement 102):441-442	Other reasons (e.g. abstract only, review)
Ngajilo, Dorothy; Singh, Tanusha; Ratshikhopha, Edith; Dayal, Payal; Matuka, Onnicah; Baatjies, Roslynn; Jeebhay, Mohamed F. Risk factors	Study exposures does not fulfil

associated with allergic sensitization and asthma phenotypes among poultry farm workers. American Journal of Industrial Medicine 2018;61(6):515-523	exposure definition
Nieuwenhuizen, Natalie E. Anisakis - immunology of a foodborne parasitosis. Parasite immunology 2016;38(9):548-557	Other reasons (e.g. abstract only, review)
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Schyllert C.; Hedman L.; Andersson M.; Hedlund U.; Lundback B.; Ronmark E.; Lindberg A. Increased risk of asthma and rhinitis after exposure to chemicals. European Respiratory Journal / 2015;46(SUPPL. 59)	Other reasons (e.g. abstract only, review)
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Soyseth, Vidar; Johnsen, Helle Laier; Henneberger, Paul K.; Kongerud,	Study exposures

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Supapvanich, Chompunuch; Povey, Andrew C.; de Vocht, Frank. Latex sensitization and risk factors in female nurses in Thai governmental hospitals. International journal of occupational medicine and environmental health 2014;27(1):93-103	Study exposures does not fulfil exposure definition
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Thanasias, E.; Polychronakis, I.; van Kampen, V.; Bruening, T.; Merget, R. Occupational Immediate-Type Allergic Asthma due to Potassium Tetrachloroplatinate in Production of Cytotoxic Drugs. Respiratory Regulation - Clinical Advances 2013;755(Journal Article):47-53	Study exposures does not fulfil exposure definition
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van der Walt, Anita; Singh, Tanusha; Baatjies, Roslynn; Lopata, Andreas Ludwig; Jeebhay, Mohamed Fareed. Work-related allergic respiratory disease and asthma in spice mill workers is associated with inhalant chili pepper and garlic exposures. Occupational and environmental medicine 2013;70(7):446-452	Study exposures does not fulfil exposure definition
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Vu, Mi; Bala, Harini Rajgopal; Cahill, Jennifer; Toholka, Ryan; Nixon, Rosemary. Immediate hypersensitivity to chlorhexidine. Australasian Journal of Dermatology 2018;59(1):55-56	Study outcome does not fulfil outcome definition
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Walters G.; Robertson A.; Moore V.; Burge S. Occupational asthma from sensitization to a chlorine-containing triclosan cleaner. European Respiratory Journal / 2014;44(SUPPL. 58)	Other reasons (e.g. abstract only, review)
Wang L.; Rosenman K. Adverse Health Outcomes Among Industrial and Occupational Sectors in Michigan. Preventing chronic disease / 2018;15((Rosenman) Department of Medicine, Michigan State University, East Lansing, MI, United States):E102	Study outcome does not fulfil outcome definition
Watanabe M.; Kurai J.; Sano H.; Torai S.; Yanase H.; Funakoshi T.; Fukada A.; Hayakawa S.; Kitano H.; Shimizu E. Prevalence of allergic rhinitis based on the SACRA questionnaire among Japanese nursing professionals with asthma. Journal of Medical Investigation / 2016;63(1-2):108-113	Other reasons (e.g. abstract only, review)
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	asthma
White, Gretchen E.; Mazurek, Jacek M.; Storey, Eileen. Employed adults with asthma who have frequent workplace exposures. Journal of Asthma 2015;52(1):46-51	Study exposures does not fulfil exposure definition
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PAPER III

Arbejdsbetinget astma: definition, forekomst, risikofaktorer, diagnose og behandling

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Dansk abstract

Arbejdsrelateret astma er hyppig. Det er derfor vigtigt at overveje en mulig sammenhæng mellem arbejde og astma hos voksne, også da det påvirker prognosen. Ved vurdering af en potentiel årsagssammenhæng overvejes om der er tilstrækkelig evidens for at den aktuelle eksponering, kan forårsage astma. Det er også afgørende, om patienten har været relevant eksponeret, og om der er andre konkurrerende årsager, som er vigtigere end den arbejdsrelaterede eksponering. Der foreligger nu opdaterede lister over potentielt sensibiliserende arbejdsrelaterede eksponeringer, som kan forårsage astma, inkl. evidensgrundlaget for hver eksponering.

English summary

Work-related asthma is common, and it is important to consider the importance of work for adult asthmatics as it affects prognosis. When assessing causation, it is important to consider the evidence for the suspected exposure with regards to its ability to cause asthma. It is also crucial to determine whether the patient has been adequately exposed and whether there are other competing risk factors that are more important than the occupational exposure. There are now updated lists of potentially sensitizing occupational exposures that can cause asthma, including the evidence level for each exposure.

Introduktion

Arbejdsrelateret astma er hyppig, og da erhvervseksponeringer kan forværre prognosen, er det vigtigt at overveje arbejdets betydning hos voksne patienter med astma. Formålet med denne statusartikel er derfor at give en opdateret oversigt over definition, forekomst, risikofaktorer, diagnostik og behandling af arbejdsrelateret astma. Formålet er også at præsentere nyligt opdaterede lister af potentielle arbejdsrelaterede sensibiliserende eksponeringer, som kan forårsage astma, inkl. evidensgrundlaget for hver eksponering.

Astma

Astma er en sygdom med anfaldvis hoste, åndenød, og pibende hvæsende vejrtrækning. Patofysiologisk er astma karakteriseret ved variabel luftvejsobstruktion, re-modellering af bronkier og bronkioler, samt persisterende luftvejsinflammation.[1] Astma optræder som oftest tidligt i barndommen, men kan debutere hele livet. Prævalensen af selvrapporteret aktuel astma blandt voksne i de nordiske lande er 5-10 % (6 % i Danmark), hvilket har været støt stigende fra 1990 til 2010 uden klar forskel for forskellige fødselsårgange (kohorteeffekt),[2] men med klare tegn på stabilisering inden for de seneste år. Incidensen af selvrapporteret astma blandt voksne i Norden er estimeret til ca. 2/1000 person-år.[3]

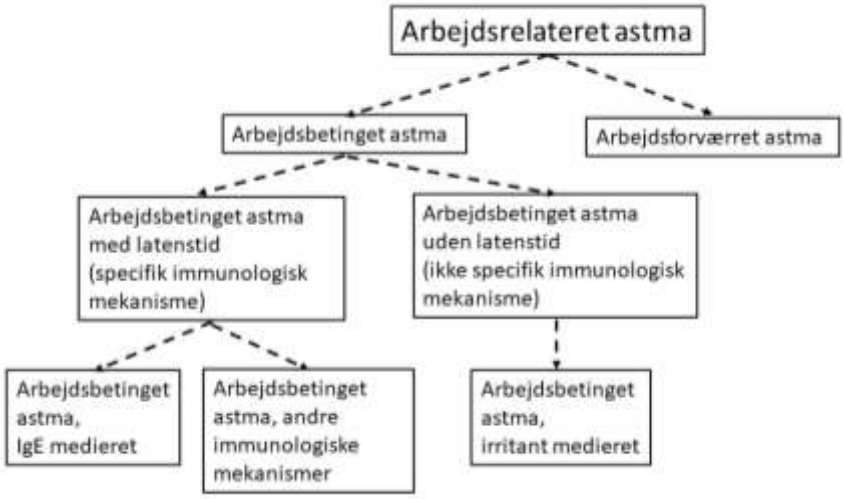
Arbejdsbetinget astma

Astma relateret til eksponeringer på arbejdspladsen opdeles sædvanligvis i arbejdsbetinget og arbejdsforværret astma (figur 1). Arbejdsbetinget astma er helt eller delvist forårsaget af eksponeringer på arbejdspladsen, mens arbejdsforværret astma er en arbejdsudløst forværring af den eksisterende astma.[4] Der findes ikke tal for omfanget af arbejdsbetinget astma i Danmark.

Baseret på primært udenlandske data skønnes det, at 15 % af astma blandt voksne skyldes eksponeringer på arbejdspladsen.[5, 6] Hvis vi antager, at disse tal er gældende for Danmark, vil vi forvente at ca. 19.000 personer i Danmark har arbejdsbetinget astma, og samtidig forvente ca. 800 nye tilfælde af arbejdsbetinget astma i Danmark per år. I beregningerne antager vi en astma-prævalens på 5 %, en årlig astma-incidens på 0,2 %, og en arbejdsstyrke på 2,5 millioner personer. Til sammenligning anmeldes årligt ca. 130 tilfælde af mulig arbejdsbetinget astma til Arbejdsmarkedets Erhvervssikring (https://www.aes.dk).

Almindeligvis inddeles arbejdsbetinget astma i tilstande opstået med eller uden en latenstid fra eksponeringsstart til sygdomsdebut (figur 1). Arbejdsbetinget astma som følge af immunologiske mekanismer opstår med latenstid, hvilket hyppigst forekommer efter eksponering for højmolekylære stoffer (f.eks. enzymer og proteiner i mel og dyreekskrementer). Ved IgE-medieret arbejdsbetinget astma ses ofte både en straks reaktion (minutter) og en senreaktion (timer til dage), domineret af henholdsvis histaminfrigørelse og et eosinofilt respons med frigivelse af leukotriener. Ikke-IgE medieret arbejdsbetinget astma udløses hovedsageligt af lavmolekylære stoffer (f.eks. isocyanater, plicatin-syre og persulfater), som forårsager en ikke-IgE medieret immunologisk reaktion,[4] og hvor en senreaktion er dominerende.

Figur 1. Skematisk oversigt over typer af arbejdsrelateret astma. Inspireret af Baur et al 2012[4]



Potentielle arbejdsrelaterede sensibiliserende eksponeringer

Sammenhængen mellem arbejdsrelaterede potentielle sensibiliserende eksponeringer og astma er blevet undersøgt i adskillige studier og inkluderer et stort antal eksponeringer. I et omfattede systematisk review, undersøgte Baur et. al. (2014)[7] evidensen for sammenhængen mellem 372 potentielle arbejdsrelaterede sensibiliserende eksponeringer og astma baseret på 865 studier. Dette review viste, at der er stærk evidens for en sammenhæng for eksponering for forskellige laboratoriedyr og moderat evidens for 35 eksponeringer. For de resterende eksponeringer fandt studiet ingen eller begrænset evidens. Vi har i 2020 gennemført et overview af systematiske reviews og et systematisk review om potentielle sensibiliserende eksponeringer som en opfølgning på Baurs review, hvilket omfattede over 1189 studier samt 486 potentielle arbejdsrelaterede sensibiliserende eksponeringer. Baseret på disse to studier, var vi i stand til at opgradere evidensen for en række eksponeringer, bl.a. konkluderede vi, at der nu foreligger stærk evidens for træstøv og svampene Aspergillus, Cladosporium og Penicllium genera og moderat moderate evidens for mider, fisk og krebsdyr samt 60 subgrupper/specifikke

eksponeringer. I tabel 1 ses oversigt over potentielle sensibiliserende eksponeringer på arbejdspladsen, som kan forårsage astma, samt evidensgrundlaget for hver eksponering.

Udredning og diagnose af mulig arbejdsbetinget astma

Udredningen af arbejdsbetinget astma består af 2 dele: a) Verificering af astmadiagnosen, og b) Verificering af arbejdsbetinget astma

a) Verificering af astma diagnose

Diagnostik af astma som mistænkes for at være forårsaget af en eksponering på arbejdspladsen adskiller sig ikke fra anden astma diagnostik. Astmalignende symptomer (periodevis natlig hoste, pibende/hvæsende vejtrækning, trykken for brystet, åndenød) er en vigtig del af diagnostikken, men diagnosen skal altid understøttes af para-kliniske undersøgelser inkl. lungefunktionsundersøgelse. Det er vigtigt, at dokumentere øget variabilitet i enten peak flow (PEF) eller FEV_1 med et positivt udfald af en eller flere af følgende undersøgelser: Reversibilitetstest med bronkodilatator og/eller kortikosteroid, daglig monitorering af PEF og FEV_1, eller uspecifik bronkial provokation med f.eks. fysisk aktivitet eller mannitol. Desuden måles NO i eksspirationsluften, som oftest er forhøjet ved ubehandlet astma. Endelig undersøges for sensibilisering over for almindeligt forekommende inhalationsallergener, da atopi er en risikofaktor for arbejdsbetinget IgE-medieret astma (jvnf. retningslinjer Dansk Lungemedicinsk Selskab, https://www.lungemedicin.dk).

b) Verificering af arbejdsbetinget astma

Når man skal vurdere om astma hos en patient er forårsaget af en eksponering på arbejdspladsen skal den udløsende eksponering identificeres, hvorefter der tages udgangspunkt i kriterier for arbejdsbetinget sygdom.[8]

1) Er der tilstrækkelig evidens for, at den eksponering man mistænker, kan være årsag til astma (videns grundlag)
2) Er mængde og type af eksponering patienten har været udsat for relevant i forhold til at kunne give astma (eksponeringsvurdering)
3) Er den tidsmæssige relation mellem eksponering og (debut af) astma relevant (eksponering før astma)?
4) Er der andre konkurrerende årsager, som er vigtigere end eksponeringen på arbejdspladsen?

<u>Tidsmæssig sammenhæng og udløsende eksponering</u>

Ved optagelse af anamnese indhentes oplysninger om erhverv, mulige eksponeringer, og arbejdsrelation (tidspunkt for debut af symptomer, færre/ingen symptomer i friperioder). Hvis der ud fra anamnesen fortsat er mistanke om astma forårsaget af eksponeringer på arbejdspladsen suppleres med en eller flere undersøgelser for at afdække sammenhængen mellem astma og arbejdsrelaterede sensibiliserende eksponeringer:

- Peak flow monitorering og FEV_1-måling: Foregår oftest via en arbejdsmedicinsk klinik. Der gennemføres typisk 3-5 ugers PEF-monitorering og/eller FEV_1-måling på faste tidspunkter mindst 5 gange/dag i personens vågne timer både i arbejds- og arbejdsfri perioder. Patienten gennemfører hver gang 3 forsøg og skriver de 2 bedste forsøg ned.

Brugen af anfalds-medicin registreres samtidigt. Der findes frit tilgængelige registreringssystemer på nettet f.eks. http://www.occupationalasthma.com/.

- Måling af uspecifik bronkial hyperreaktivitet i arbejds- og arbejdsfri perioder for at påvise en evt. forskel.
- Priktest, specifikt IgE, histamine release test eller basofil aktiveringstest overfor mistænkte sensibiliserende eksponeringer på arbejdspladsen. Der kan rekvireres test overfor en række kommercielt tilgængelige arbejdsrelaterede sensibiliserende eksponeringer fra ThermoFischer/Phadia (http://www.phadia.com/Global/A%20Document%20Library/Product%20Catalogues/Product-Catalog-2018.pdf). Flere større sygehuse i Danmark tilbyder internt Specifik IgE for en række eksponeringer på arbejdspladsen samt basofil aktiveringstest. Ved høj-molekylære sensibiliserende eksponeringer kan det af og til være hensigtsmæssigt at prikteste med materiale fra arbejdspladsen, ligesom der kan sendes materiale fra arbejdspladsen til Reference Laboratoriet (www.reflab.dk) med henblik på histamin release test.

Hvis den kausale sammenhæng er usikker, kan der suppleres med specifik inhalations provokation (specific inhalation challange, SIC).[9, 10] Ved SIC udsættes patienten for den mistænkte eksponering under kontrollerede forhold og under akut beredskab. Aktuelt foretages SIC på de tre Allergicentre i Danmark med højt specialiseret funktion (Odense Universitetshospital, Aarhus Universitetshospital, og Gentofte Hospital). For at vurdere om SIC understøtter årsagssammenhæng er det vigtigt,

a) At der bruges realistiske eksponeringsniveauer
b) At der eksponeres for flere niveauer for at kunne vurdere dosis-respons relation og evt. tærskelværdi
c) At der bruges en relevant kontroleksponering (negativ kontrol) i forhold til den "aktive" eksponering, og at der ikke er kraftig forøget bronkial hyper-reaktivitet på undersøgelsestidspunktet.
d) At patienten blindes for om eksponeringen er negativ kontrol eller aktiv eksponering

Jo flere af ovenstående punkter der opfyldes, jo større tiltro kan man have til at en given positiv provokation afspejler en kausal sammenhæng mellem eksponering og astma.

Optimal medicinsk behandling

Den medicinske behandling for arbejdsbetinget astma er den samme som for astma generelt.

Ophør eller minimering af eksponering

En række studier tyder på, at eksponeringer på arbejdspladsen hænger sammen med en dårligere reguleret astma .[11] Prognosen for arbejdsbetinget astma er formentlig bedst hvis patienten helt undgår den relevante eksponering,[12] hvilket i praksis betyder, at de fleste må skifte arbejdsplads og muligvis erhverv. Dette har ofte store sociale og økonomiske omkostninger for den enkelte, og derfor bør man forsøge om patienten kan forblive i arbejdet ved omlægninger i arbejdsopgaver eller produktion, som gør at eksponeringen minimeres eller fjernes. Som ved andre mistænkte erhvervsbetingede sygsomme skal der foretages anmeldelse til Arbejdsmarkedets erhvervssikring (https://www.aes.dk). Anmeldelsen kan ske af patienten selv, men vil typisk foretages af egen læge. Hvis patienten henvises til en arbejdsmedicinsk klinik eller ses på lungemedicinsk afdeling vil anmeldelse typisk ske dér.

Tabel 1: Oversigt over potentielle sensibiliserende eksponeringer på arbejdspladsen

Evidens niveau	Hoved og undergrupper/specifikke eksponeringer
Stærk	*Hovedgruppe:* Træstøv* *Undergrupper/specifikke eksponeringer:* Aktiviteter på arbejde: Arbejde med forsøgsdyr
Moderat	*Hovedgruppe:* Krebsdyr, enzymer, fisk, mider *Undergrupper/specifikke eksponeringer:* Fisk: Atlanterhavs-laks, "seafood" fiskemel, ørred/fore, pighvar Insekter: Græshoppe/cicade, silkeorm Krebsdyr: Rejer, sne krabber (snow crab) Mider: Rovmider, spindemider, lagermider Pattedyr: Køer, rotter Produkter fra dyr: Ægge protein Planter: Ubehandlede kaffebønner, latex, paprika, psyllium, tobak, diverse the støv, kæmpetuja Biocider: Pesticider Syre anhydrider: Pthal syre anhydrid Andre kemiske eksponeringer: Akrylater, rengøringsspray: blegemiddel, disinfektionsprodukter, kloramine, kloramine-T, kvaternære ammonium forbindelser, formaldehyd, glutaraldehyd Medicin: Morfinpræparater Maling/farver: Karmin farver, reaktive farvestoffer Enzymer: a-amylase fra Aspergillus oryzae, enzymer i vaskemidler, papain, phytase fra Aspergillus niger, diverse enzymer fra Bacikkus subtilis Svampe: Aspergillus, Cladosporium, Penicllium arter Isocyanater:** Methylen diphenyl-diisocyant, toluen diisocyanat, diverse andre isocyanater Metaller: Platin salte Aktiviteter på arbejde: Landbrug (husdyr, korn, hø/halm, lagermider), bagerier (mel, amylase, lagermider), og forarbejdning af soyabønner (bælg, mel, enzymer)
Begrænset/in-konsistent	*Main group:* Anhydrider, fugle, maling/farver, pattedyr, metaller, svampe inkl. skimmelsvampe og gærsvampe, andre spindlere, andre kemiske produkter (f.eks. reaktive kemikalier)
Ingen videnskabelig evidens	*Main group:* Aminer, biocider, padder, produkter fra dyr, medicin, insekter, bløddyr, planter (ikke træstøv)

Grupperingen af ovennævnte potentieller arbejdsrelaterede sensibiliserende eksponeringer er foretaget efter grupperingen i Baur et. al. (2014)

* Evidensen for specifikke typer af træstøv spreder sig fra ingen til moderat evidens. For flere detaljer, se venligst Dalbøge et. al. 2020 og Schlünssen et. al. 2012

** Isocyanater er i Baur et. al. (2014) en selvstændig gruppe under "biocider og kemiske stoffer"

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External evaluation of the reference document on occupational sensitizers and asthma

Background

The *National Board of Industrial Injuries and the Occupational Diseases Committee* in Denmark requested a detailed scientific reference document of the causality between potential occupational sensitizing exposures and the development of asthma. This work has been headed by researchers from the *Danish Ramazzini Centre* (Aarhus University). Undersigned have acted as external experts during the study process and have reviewed the reference document. In this brief evaluation we would like to reflect on the relevance, the quality and the challenges of the document.

Relevance: Occupational asthma is a preventable disease

Asthma is a common disease in both children and adults. It has been estimated that occupational exposures account for about 15% of new adult asthma cases. These are modifiable risk factors, and hence a relevant proportion of adult asthma cases might be prevented when exposures in the workplace are controlled. Hundreds of different occupational agents have been suggested to be potentially able to cause asthma. By far most of these agents are high or low molecular weight sensitizers. The level of evidence is highly variable across the different agents, mostly deriving from clinical (case) studies and to a lesser extent from epidemiological studies. A systematic overview of the existing evidence for all suspected agents (or groups of agents) was urgently needed, in particular for those suspected occupational sensitizing exposures with apparently insufficient evidence. In addition, there is a need for guidelines for clinical evaluation of patients with (suspected) asthma that may be caused by exposure to sensitizers in their workplaces. This may help to detect work-related asthma in an early stage and prevent further exacerbation of the disease and limit disability.

Quality: Systematic and comprehensive inventory, review, quality assessment and synthetization of published studies

First, an overview of systematic reviews was performed and the scientific quality of the reviews was assessed by a systematic evaluation using established criteria. Over 2000 potentially relevant articles were identified, and after systematic quality evaluation 22 systematic reviews were included. Most reviews were rated as having low confidence; only three and five reviews had high and moderate confidence, respectively. These reviews covered 1000 studies and 500 (sensitizing) exposures. The quality of the evidence was rated for each agent.
Based on the knowledge gap identified in the overview a systematic review was performed of the relation between 10 selected potential occupational sensitizing exposures and asthma.
Based on the quality and quantity of the included studies, the level of evidence were upgraded or downgraded for both main groups of exposure, as well as for subgroups/specific exposures.

Challenges: Different types of studies and evidence for a multitude of workplace exposures and agents with different possible effect mechanisms

The scientific evidence is based on mainly case studies or series, and epidemiological studies. One challenge is to evaluate the quality of both study types with the same method. It should also be

considered that the evidence for an individual agent being an (occupational) sensitizer is typically based on clinical studies rather than epidemiological studies and is not generalisable to groups of agents. Epidemiological studies are important to show excess risks of asthma among workers exposed to mostly groups of agents, often mixtures. A final challenge is that agents may cause (occupational) asthma by different effect mechanisms. Most agents will act through an allergic mechanism (high or low molecular weight sensitizers), but there is increasing evidence that agents can (also) cause asthma through an irritative mechanism. The evidence is not easy comparable for both types, and the irritative mechanism often refers to groups of agents (or heterogeneous mixtures) without the identification of a single responsible agent.

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