ONLINE SUPPLEMENTARY MATERIAL

Online supplementary TABLE sO1 Mesh terms and their combinations used for literature search of individual key questions and ancillary questions

KQ = Key question

Initial search date	sub topic	search term	initial hits (2008)	final hits (04/2010)
KQ 1: "How are and should WRA cases be diagnosed?"				
7/31/2008	KQ1 - diagnostics	Asthma[Majr] AND "Occupational Diseases"[Mesh] AND ("Diagnosis"[Majr] OR "Diagnostic Techniques, Respiratory System"[Mesh]) AND (("2004/01/01"[PDAT] : "2099/07/30"[PDAT]) AND "humans"[MeSH Terms] AND "adult"[MeSH Terms])	88	134
KQ 2: "What are the risk factors – host and exposure – for a bad outcome?"				
1/24/2008	KQ2 a - general risk factors (exposure type)	"Risk factors"[Mesh] AND ("prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up studies"[Mesh]) AND "Asthma"[Mesh] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational	56	64

		exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "Occupational"[all] OR "work related"[all] OR "work aggravated"[All] OR "Workplace"[All] OR "work site"[All] OR "occupational agent"[all] OR "work related agent"[all] OR "Job"[All]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh])		
2/25/2008	KQ2 b - duration	("duration of exposure"[all] OR "exposure duration"[all] OR "exposure cessation"[all] or "long-term cessation"[all]) AND ("prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up studies"[Mesh] OR "Recovery of Function"[Mesh]) AND "Asthma"[Mesh] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "work related"[all] OR "work aggravated"[All]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh] OR "Risk factors"[Mesh])	18	18

2/21/2008	KQ2 e - atopy	("atopy"[all] OR "atopic status"[all]) AND ("prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up studies"[Mesh]) AND "Asthma"[Mesh] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "work related"[all] OR "work aggravated"[All]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh] OR "Risk factors"[Mesh])	15	17
2/21/2008	KQ2 h - airway inflammation	"airway inflammation"[all] AND ("prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up studies"[Mesh]) AND "Asthma"[Mesh] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "work related"[all] OR "work aggravated"[All])	17	18

		AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh])		
2/21/2008	KQ2 d - smoking	("Smoking"[Mesh] OR "Tobacco Smoke Pollution"[Mesh] OR "Tobacco Use Cessation"[Mesh]) AND ("prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up studies"[Mesh]) AND "Asthma"[Mesh] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "work related"[all] OR "work aggravated"[All]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh] OR "Risk factors"[Mesh])	20	25
2/21/2008	KQ2 f - impaired lung function	("Respiratory function tests"[Mesh] AND ("impairment"[all] OR "decrease"[all] OR "decline"[all] OR "lower"[all])) AND ("prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up	38	39

		studies"[Mesh]) AND "Asthma"[Mesh] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "work related"[all] OR "work aggravated"[All]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh] OR "Risk factors"[Mesh])		
KQ 3: "What is the outcome of different management options in already affected subjects?"				
	Ancillary question 1: "What is the effectiveness of complete exposure avoidance?"- related to Rachiotis et al. and update search from 2004			
9/08/2009	KQ3 a - complete exposure avoidance since 2004	"Asthma"[Mesh] AND "Occupational Diseases"[Mesh] AND ("Follow-Up Studies"[Mesh] OR "Prognosis"[Mesh] OR "Time Factors"[Mesh]) AND (("2004/01/01"[PDAT] : "2009/09/09"[PDAT]) AND "humans"[MeSH Terms] AND "adult"[MeSH Terms])	48	50
	Ancillary question 2: "What is the effectiveness of reduced exposure?"			
2/20/2009	KQ3 b - exposure reduction (generall)	("Asthma"[Mesh] OR "Hypersensitivity"[Mesh]) AND ("Occupational exposure"[Mesh] OR "Occupational Diseases"[Mesh] OR "occupational"[all]) AND (("reduction"[all] OR	76	80

		"reduced"[all] OR "reducing"[all] OR "limitation"[all] OR "limited"[all]) AND "exposure"[all]) AND ("Prognosis"[Mesh] OR "Outcome Assessment (Health Care)"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "Follow-Up Studies"[Mesh] OR "Quality of Life"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up"[all] OR "time factors"[Mesh]) AND "humans"[MeSH Terms] AND "adult"[MeSH Terms] NOT "infant"[Mesh]		
1/14/2008	KQ3 b 1&2 - engineering control or relocation	("Occupational Exposure"[Mesh] OR "Occupational Diseases"[Mesh] OR "Occupational"[all] OR "work related"[all] OR "work aggravated"[All] OR "Workplace"[All] OR "work site"[All] OR "occupational agent"[all] OR "Job"[All]) AND ("prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "Quality of Life"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up studies"[Mesh] OR "Controlled Clinical Trial "[Publication Type]) AND ("Threshold Limit Values"[Mesh] OR "exposure reduction"[all] OR "reduced exposure"[all] OR	66	70

		"engineering control"[all] OR "relocation"[all] OR "prevention and control "[Subheading] OR "exposure avoidance"[all] OR "exposure cessation"[all] OR "exposure control"[all]) AND ("Asthma"[Mesh] OR "Hypersensitivity"[Mesh] OR "Hypersensitivity, Immediate"[Mesh]) AND ("humans"[MeSH Terms] AND "adult"[MeSH Terms])		
1/24/2008	KQ3 b 3 - PPE	("Respiratory Protective Devices"[Mesh] OR "Head protective devices"[Mesh]) AND ("Asthma"[Mesh] OR "Hypersensitivity"[Mesh] OR "Hypersensitivity, Immediate"[Mesh]) AND ("Occupational"[all] OR "work related"[all] OR "work aggravated"[All] OR "Workplace"[All] OR "work site"[All] OR "occupational agent"[all] OR "work related agent"[all] OR "Job"[All])	25	28
	Ancillary question 3: "Is it possible to reduce symptoms / improve lung function by pharmacological treatment in connection with an ongoing exposure?"			
2/21/2008	KQ3 c 1 - ICS	("Adrenal Cortex Hormones"[Mesh] OR "Glucocorticoids"[Mesh] OR "Glucocorticoids "[Pharmacological Action]) AND ("prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "Quality	15	19

		of Life"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up studies"[Mesh] OR "Controlled Clinical Trial "[Publication Type]) AND ("Asthma"[Mesh] OR "Hypersensitivity"[Mesh] OR "Hypersensitivity, Immediate"[Mesh]) AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh] OR "Farmer's Lung"[Mesh] OR "Skin Diseases"[Mesh] OR "Alveolitis, Extrinsic Allergic"[Mesh] OR "Pulmonary Fibrosis"[Mesh])		
2/14/2008	KQ3 c 2 - beta agonists	("Adrenergic beta-Agonists"[Mesh] OR "Sympathomimetics"[Mesh] OR "Bronchodilator Agents"[Mesh] OR "Adrenergic beta-Agonists "[Pharmacological Action]) AND ("prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up studies"[Mesh]) AND ("Asthma"[Mesh] OR "Hypersensitivity"[Mesh] OR "Hypersensitivity,	16	20

		Immediate"[Mesh]) AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "Occupational"[all] OR "work related"[all] OR "work aggravated"[All] OR "Workplace"[All] OR "work site"[All] OR "occupational agent"[all] OR "work related agent"[all] OR "Job"[All]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh])		
2/21/2008	KQ3 c 3 - other drugs	("Anti-Asthmatic Agents"[Mesh] OR "Drug Therapy"[Mesh] OR "Medication Therapy Management"[Mesh] OR "Administration, Inhalation"[Mesh]) AND ("prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up studies"[Mesh]) AND ("Asthma"[Mesh] OR "Hypersensitivity"[Mesh] OR "Hypersensitivity, Immediate"[Mesh]) AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh]) AND	22	39

		"humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh] OR "Adrenergic beta-Agonists"[Mesh] OR "Adrenal Cortex Hormones"[Mesh] OR "Glucocorticoids"[Pharmacological Action] OR "Adrenergic beta-Agonists"[Pharmacological Action])		
9/09/2009	KQ3 c 4 - immuno therapy	"Occupational Diseases"[Mesh] AND "Asthma"[Mesh] AND "Immunotherapy"[Mesh] AND ("1984/09/09"[PDAT] : "2012/09/09"[PDAT]) AND "humans"[MeSH Terms] AND "adult"[MeSH Terms]	24	24
KQ 4 : "What are the benefits of medical screening and surveillance?"				
5/09/2008	KQ4 - medical screening	("Mass Screening"[Mesh] OR "screening"[all]) AND "Asthma"[Mesh] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "work related"[all] OR "work aggravated"[All]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh])	75	79

8/26/2008	KQ4 - medical surveillance	("Safety Management"[Mesh] OR "Population Surveillance"[Mesh] OR "epidemiology "[Subheading]) AND "Asthma"[Mesh] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "work related"[all] OR "work aggravated"[All]) AND ("prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "Quality of Life"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up studies"[Mesh] OR "Controlled Clinical Trial "[Publication Type]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh]) AND "adult"[MeSH]	18 / 62	73
KQ 5: "What is the impact of controlling work-related exposures to prevent asthma?"				
6/16/2008	KQ5 - outcome and control	("primary prevention"[Mesh Terms] OR ("prevention and control"[Subheading] AND "Environmental Exposure"[Mesh])) AND "Asthma"[Mesh] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh]) AND	72	78

		"humans"[MeSH Terms] AND "adult"[MeSH Terms] AND "adult"[MeSH Terms]		

Online supplementary TABLE sO2 Supplemental search strategy for literature search for each key question and ancillary question

Supplemental literature searches by the individual expert groups			
search date / period	sub topic	search term / key words	additional findings (date)
KQ 1: „How are and should WRA cases be diagnosed?“			
07/2008 2004-2010	Diagnostics ancillary questions	Asthma[Majr] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "work related"[all] OR "work aggravated"[All]) AND ("Diagnosis"[Majr] OR "Diagnostic Techniques, Respiratory System"[Mesh]) AND (("2004/01/01"[PDAT] : "2099/07/30"[PDAT]) AND "humans"[MeSH Terms] AND "adult"[MeSH Terms]) Limits: Publication Date to 2010/04.	203
KQ 2: „What are the risk factors – host and exposure – for a bad outcome?”			
2008 - 2010	General risk factors	Risk factors"[Mesh] AND ("prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up studies"[Mesh]) AND "Asthma"[Mesh] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational	0

		exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "work related"[all] OR "work aggravated"[All]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh]	
2008 - 2010	Smoking:	("Smoking"[Mesh] OR "Tobacco Smoke Pollution"[Mesh] OR "Tobacco Use Cessation"[Mesh]) AND ("prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up studies"[Mesh]) AND "Asthma"[Mesh] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "work related"[all] OR "work aggravated"[All]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh] OR "Risk factors"[Mesh]) AND "Asthma"[Mesh] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "work related"[all] OR "work aggravated"[All]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh] OR "Risk factors"[Mesh])	0

2008 - 2010	Atopy:	("atopy"[all] OR "atopic status"[all]) AND ("prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up studies"[Mesh]) AND "Asthma"[Mesh] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "work related"[all] OR "work aggravated"[All]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh] OR "Risk factors"[Mesh]) AND "Asthma"[Mesh] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "work related"[all] OR "work aggravated"[All]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh] OR "Risk factors"[Mesh])	0
2008 - 2010	Duration and cessation:	("duration of exposure"[all] OR "exposure duration"[all] OR "exposure cessation"[all] or "long-term cessation"[all]) AND ("prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up studies"[Mesh] OR "Recovery of Function"[Mesh]) "Asthma"[Mesh] AND	0

		("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "work related"[all] OR "work aggravated"[All]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh] OR "Risk factors"[Mesh]) AND "Asthma"[Mesh] AND ("occupational diseases"[Mesh] OR "occupational health"[Mesh] OR "occupational exposure"[Mesh] OR "occupational groups"[Mesh] OR "workplace"[Mesh] OR "work related"[all] OR "work aggravated"[All]) AND "humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh] OR "Risk factors"[Mesh])	
KQ 3: „What is the outcome of different management options in already affected subjects?“			
-	Management of WAR	no supplemental search performed	
KQ 4: „What are the benefits of medical screening and surveillance?“			
-	medical screening	no supplemental search performed	-
KQ 4: „What are the benefits of medical screening and surveillance?“			

5/07/2009	medical surveillance	"Occupational Exposure"[Mesh] OR "Occupational Diseases"[Mesh] OR "Occupational"[all] OR "work related"[all] OR "work aggravated"[All] OR "Workplace"[All] OR "work site"[All] OR "occupational agent"[all] OR "Job"[All] AND "prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "Quality of Life"[Mesh] OR "outcome"[all] OR "prognosis"[all] OR "prognostic value"[all] OR "follow-up studies"[Mesh] OR "Controlled Clinical Trial "[Publication Type] AND "Asthma"[Mesh] OR "Hypersensitivity"[Mesh] OR "Hypersensitivity, Immediate"[Mesh] AND "Occupational"[all] OR "work related"[all] OR "work aggravated"[All] OR "Workplace"[All] OR "work site"[All] OR "occupational agent"[all] OR "work related agent"[all] OR "Job"[All] AND "Population Surveillance"[Mesh] OR "Sentinel Surveillance"[Mesh] OR "Safety Management"[Mesh])	23
5/07/2009	medical surveillance	Search own archive	17
KQ 5: „What is the impact of controlling work-related exposures to prevent asthma?"			
03/2010	Respirators in primary prevention	"Air Pollutants, Occupational"[Mesh] AND "Respiratory Protective Devices"[Mesh] AND ("Asthma"[Mesh] OR "Occupational Exposure/prevention and control"[Mesh]) AND "humans"[MeSH Terms] Respirators in primary	77 (13 selected)

03/2010	Skin exposure and prevention	(“skin” [all] OR “dermal”[all]) AND (“occupational diseases”[all] OR “occupational exposures”[all] OR “isocyanates”[all] OR “diisocyanates”[all]) AND “asthma”[all] AND “human”[all]	44 (15 selected)

Online supplementary TABLE sO3 Evidence Tables for KQ 2 – 5

Author / year	Authors main conclusion	SIGN grade	Study type	Exposure /occupation	Subjects (n)
Chapter 1: Contribution of host factors and workplace exposure to the outcome of occupational asthma (for more details including elaboration of references see [1]					
Allard 1989 [2]	Duration of exposure after onset of symptoms was negatively correlated to PC20 at second follow-up. Total duration of exposure was negatively correlated to changes in PC20 between baseline and second follow-up. There was not significant correlation between duration of exposure and baseline lung function or lung function at follow-up. In general no improvement was seen among OA patients after several years of exposure cessation.	2-	Longitudinal	Various HMW and LMW agents	28
Anees 2006 [3]	FEV1 declines rapidly (101 ml/year) in OA subjects still exposed compared to OA subjects not exposed anymore (27 ml/year). Baseline age, sex, baseline FEV1, current smoking, and use of steroids was not associated to decline in FEV1. Mean step-up of FEV1 (during 1 year after removal from exposure) is not related to age, atopic status, smoking, latent interval between first exposure and first symptoms, duration of symptomatic exposuree, initial FEV1% predicted. There's not influence of therapy with steroids. Mean decline of FEV1 after removal from exposure is not related to duration of symptomatic exposure or latent interval between first	2+	Longitudinal	Various HMW and LMW agents	156

	exposure and first symptoms, nor with smoking status.				
Chang-Yeung 1977 [4]	Most patients with occupational asthma due to Thuja Plicata recover after leaving the industry and above all nonsmokers, but BHR, irrespective of symptoms, persist after cessation of exposure.	2-	Longitudinal	Western red cedar	38
Chang-Yeung 1982 [5]	Symptoms after a follow up of 3.5 yrs are worse when continuing exposure. Among no longer exposed there's a worse outcome when there are: older age, longer duration of exposure before the onset of symptoms, longer duration of symptoms before diagnosis, worse lung function and higher BHR at diagnosis.	2-	Longitudinal	Western red cedar	125
Cote 1990 [6]	Subjects who deteriorated had stronger early and late asthmatic reactions to SIC with plicatic acid. They also had no different symptoms, medications, FEV1, FVC, PC20 vs subjects who didn't deteriorated. Atopy and smoking were not risk factors for a bad outcome at follow up.	2+	Longitudinal	Plicatic acid (Western red cedar)	48
Descatha 2007 [7]	Outcome is worse when there's a longer latency period. Not significant to outcome are: smoking habits, atopy and molecular weight of causal agent.	2+	Case series	various HMW and LMW agents	227
Gassert 1998 [8]	Women and industrial sector workers were at increase risk of severe asthma at follow up. Smoking at baseline was not associated to severity of asthma at follow-up.	2-	Longitudinal	Various	55
Hudson 1985 [9]	Patients with crab OA had significantly improved PC20 at follow-up, this was not the case for patients with OA due to various agents. Duration of exposure after onset of symptoms is significantly longer and FEV1 is significantly lower (at initial and follow-up evaluation) in patients with	2-	Longitudinal	Crab; various HMW and LMW agents	63

	poorer prognosis of both groups (respectively in symptomatic subjects among patients with asthma due to crab, and in subjects requiring medication among patients with asthma due to various agents).				
Labrecque 2006 [10]	A lower BHR and a worse FEV1 at diagnosis are related to a worse outcome. A longer exposure relates to a poorer prognosis.	2-	Longitudinal	Isocyanates	79
Lemière 1996 [11]	To the outcome are not relevant: clinical improvement, molecular weight of causing agent, specific Abs, duration of exposure, type of asthmatic reaction.	3	Longitudinal	various HMW and LMW agents	15
Lozewicz 1987 [12]	Patients with poorer outcome (treatment once per week or more often) had increased BHR and decreased FEV1 at baseline compared with patients with better outcome (treatment less than once per week). No association between outcome and duration of exposure, atopy, smoking, and if the patients were relocated at work or left the factory.	2+	Longitudinal	Isocyanates (TDI, MDI)	56
Maghni 2004 [13]	PC20 at follow-up is significantly associated with baseline PC20 and with time lapse since diagnosis. Patients considered 'cured'(with normal PC20 at follow-up) have significantly longer time laps since diagnosis and higer PC20 at time of diagnosis than 'not improved' and 'improved' patients. 32.1% with no improvement vs.10.7% subjects with improvement had increased sputum eosinophils. 39.3% with no improvement vs. 19.6% with improvement showed increased sputum neutrophils Levels of interleukin-8 and of the neutrophil-derived myeloperoxidase were significantly more elevated in sputum of subjects with no	2+	Longitudinal	various HMW and LMW agents	133

	improvement.				
Malo 2004 [14]	Factors significantly related with rapid recovery of bronchial responsiveness to methacholine in the first 2,5 y after cessation of exposure are: sex (the process results more rapid in females), PC20 and FEV1 at diagnosis. Recovery was not related to duration of exposure, molecular weight for asthmatogen, smoking habits or use of steorids at baseline.	2+	Longitudinal	various HMW and LMW agents	80
Mapp 1988 [15]	No significant differences between subjects who recover and those who don't with regard to age, smoking, atopy, duration of symptoms, baseline FEV1 and PD20 methacholine. Late asthmatic response (at diagnosis) is significantly higher in subjects who fail to recover. Severity of dual reaction (at diagnosis) in subjects who don't recover is significantly higher compared to subjects with dual reaction who recover.	2-	Longitudinal	TDI	35
Marabini 1993 [16]	Persistence of exposure significantly correlates with symptoms as weezing and shortness of breath, with medication score and severity of asthma at follow-up: persistence of exposure results in a deterioration in the asthma despite the use of more medications.	2-	Longitudinal	Plicatic acid (Western red cedar)	128
Marabini 1994 [17]	No significant differences have been found in symptoms prevalence or in lung function between exposed and not exposed subjects at follow-up. Persistence of exposure at follow-up is correlated (in both exposed and not exposed subjects) with significant reduction of FVC. Subjects with late response to SBPT present at follow-up a significative reduction of FVC and FEV1.	2+	Longitudinal	TDI	40

Merget 1994 [18]	Smoking, time from onset of symptoms to removal, positive skin test for environmental allergens did not influence the change in BHR between baseline and follow up.	2-	Longitudinal	Platinum salts	24
Merget 1999 [19]	Subjects still employed in production had more symptoms and more sensitization compared to subjects with less or no exposure, but no difference between low exposed and no exposed. There is a positive association between exposure and FEV1 and between duration of symptoms in high exposure areas and bronchial hyperresponsiveness to methacholine.	3	Longitudinal	Platinium salts	83
Merget 2000 [20]	A new positive skin prick test to platinum in the follow-up period was seen in the highest exposure group. Among high exposed, smoking was a risk factor for sensitization, but atopy or BHR was not.	2-	Cohort	Platinum salts	275
Moscato 1993 [21]	A lower duration of a total exposure relates to a better outcome. Also younger age, longer avoidance, better baseline FEV1 are related to a better outcome.	2+	Longitudinal	Various	29
Orriols 1999 [22]	Longer exposure relates to worse outcome. Cessation of exposure improves the outcome and lung function.	3	Longitudinal	Isocyanates	21
Padoan 2003 [23]	There is a better outcome (and higher PD20 at follow up) when: there are better lung function and lower degree of airway responsiveness to methacholine at diagnosis; there's a longer interval from cessation of exposure.	2++	Longitudinal	TDI	87
Park 1997 [24]	A better outcome (remission or improvement) is related to: shorter duration of symptoms before diagnosis, a short time lag between diagnosis and removal from exposure, milder degree of BHR at diagnosis, maybe specific IgE due to TDI-	2-	Longitudinal	TDI	35

	HAS and duration of exposure before symptoms ($p < 0.1$). Smoking and atopic status are not related to the outcome.				
Park 2002 [25]	Favourable outcome is related to shorter duration of exposure after onset of symptoms and a higher initial PC20. Age, sex, atopy, duration of exposure and type of asthmatic response during TDI-BPT not appear to be important factors for remission of disease. Significant difference of level of IgE in group with improvement of symptoms compared to no improvement group - high level of IgE at diagnosis as marker of better prognosis. Significant difference of level of IgG in group with improvement of symptoms compared to no improvement group - high level of IgG at diagnosis as marker of worse prognosis.	2-	Longitudinal	TDI	41
Perfetti 1998 [26]	A better BHR at follow-up was found in case of: higher BHR at diagnosis, shorter exposure, longer removal from exposure and better baseline FEV1. A worse PC20 at follow-up was related negatively to HMW agents and longer duration of exposure.	2-	Longitudinal	various HMW and LMW agents	99
Pisati 1993 [27]	Complete removal from exposure and early diagnosis relate to a better outcome of asthma due to isocyanate. In no longer exposed group type of reaction, duration of exposure and duration of symptomatic period aren't relevant.	2+	Longitudinal	TDI	60
Pisati 2007 [28]	A longer symptomatic exposure relates to a worse outcome. The following determinants are not relevant to a worse outcome: duration of exposure before the onset o symptoms, PD20, VC and FEV1 at baseline.	2-	Longitudinal	TDI	25

Rachiotis 2007 [29]	Symptom outcome worsens with increasing age at diagnosis and longer duration of symptomatic exposure. Persistent BHR was found in asthma related to High molecular weight agents and in Canada more than in Europe.	1-	Systematic review	Various	2376
Saric 1991 [30]	Severity of symptoms and BHR is not related to duration of exposure.	3	Longitudinal	Fluoride/SO2	30
Sorgdrager 2001 [31]	A worse FEV1 at follow-up was related to: worse baseline FEV1, longer exposure time (more than 1 yr) and smoking.	2-	Longitudinal	Fluorides	122
Soyseth 1995 [32]	BHR is lower at the follow up visit if: there's an higher initial BHR; patients take anti asthmatic treatment; patients are removed from exposure. Smoking, FEV1 and duration of exposure are not relevant to the outcome.	2+	Longitudinal	Fluorides	38
Tarlo 1997 [33]	A better outcome was found when there were: shorter symptomatic period, shorter total exposure, higher PC20 at diagnosis, better baseline spirometry. A worse outcome was related to continuing exposure. The type of isocyanate and of reaction were not relevant to the outcome.	3	Descriptive study of disease register	Isocyanates	235
Valentino 2002 [34]	Removal from exposure relates to a better outcome. In removed workers, the following topics are not relevant to the outcome: type of asthmatic reaction, duration of exposure, duration of symptomatic period, smoking and atopy.	2+	Longitudinal	TDI	50
Chapter 2: What is the optimal management option in occupational asthma? (for more details including elaboration of references see [35])					
Ancillary question 1. "What are the consequences of persistent exposure to the causal agent?"					
Anees 2006 [3]	FEV1 measurements for at least 1 year before removal from exposure. FEV1 declines rapidly in exposed workers with occupational asthma with a mean (SE) rate of decline in FEV1 was 100.9 (17.7)	2-	Longitudinal follow-up	Occupational asthma due to various agents	90

	ml/year.				
Chan-Yeung 1987 [36]	All patients with continued exposure had respiratory symptoms and required medication while 40% recovered completely among those who avoided exposure.	2-	Longitudinal follow-up	Red cedar	Avoidance of exposure (136); persistence of exposure (54); reduced exposure (42)
Gannon 1993 [37]	Workers who remained exposed had more symptoms, took more often inhaled corticosteroids, and showed a greater fall in FEV1.	2-	Longitudinal follow-up	Various agents	Avoidance of exposure (78); persistence of exposure (34)
Lin 1996 [38]	Patients who remained exposed showed a greater decline in FEV1 than sawmill workers.	2-	Longitudinal follow-up (comparison with a control population of sawmill workers)	Red cedar	Avoidance of exposure (109); persistence of exposure (92; sawmill workers (399))
Merget 1999 [19]	Workers who remained exposed experienced asthma symptoms.	2-	Cross-sectional retrospective survey	Platinum salts	Avoidance of exposure (58); persistence of exposure (9); reduction of exposure (16)
Moscato 1993 [21]	All patients who remained exposed were still symptomatic and required pharmacologic treatment.	2-	Longitudinal follow-up	Various agents	Avoidance of exposure (18); persistence of exposure (4); reduction of exposure (7)
Orriols 1999 [22]	Workers who remained exposed became clinically and functionally worse.	2-	Longitudinal follow-up	Isocyanates (various occupations)	Avoidance of exposure (17); persistence of exposure (4)
Padoan 2003 [23]	A more favourable prognosis was associated with a better lung function and a lower degree of airway hyperresponsiveness to methacholine at diagnosis	2-	Longitudinal follow-up	Isocyanates (TDI)-(various occupations)	Avoidance of exposure (74); persistence of exposure (13) but no distinction between complete persistence and reduction of exposure
Rosenberg 1987 [39]	Patients who remained exposed to the same work conditions experienced unchanged or worse respiratory symptoms. Patients who became asymptomatic after cessation or reduction of exposure were	2-	Longitudinal follow-up	Isocyanates (various occupations)	Avoidance of exposure (20); persistence of exposure (4)

	younger and had a shorter duration of symptomatic exposure.				
Tarlo 1997 [33]	None of the subjects who stayed at the same work recovered and 4/10 worsened.	2-	Retrospective review	Isocyanates (compensated cases with various occupations)	Avoidance of exposure (126); persistence of exposure (10)
Valentino 2002 [34]	The condition of subjects with persistent exposure deteriorated significantly during the follow-up period in terms of symptoms, pulmonary function parameters, PD20 and use of medications	2-	Longitudinal follow-up	Isocyanates (various occupations)	Avoidance of exposure (37); persistence of exposure (13) but no distinction between complete persistence and reduction of exposure
Ancillary question 2. "Is it possible to improve symptoms and lung function by pharmacological treatment in affected workers with persistent exposure?"					
Anees 2006 [3]	The decline in FEV1 before removal from exposure was not significantly affected by the use of inhaled corticosteroids.	2+	Retrospective cohort	Various agents	90
Marabini 2003 [40]	Observational study of 10 subjects with OA who remained exposed and were treated with beclomethasone dipropionate (500 mcg bid) and salmeterol (50 mcg bid) over 3 years Treatment with inhaled corticosteroids and long-acting bronchodilators seems to prevent respiratory deterioration over a 3-year period.	2-	Uncontrolled, non-randomized intervention	Various agents	10
Ancillary question 3. "What is the effectiveness of complete avoidance of exposure?"					
Beach 2005 [41]	Most of the studies (23 of 30) documented an improvement in asthma symptoms, but only few (3 of 30) reported complete resolution of symptoms in the majority of the subjects. An improvement in non-specific bronchial hyper-responsiveness was reported in 14 of 15 studies and an increase in the mean FEV1 in 8 of 17 studies. However, a substantial proportion of the subjects, ranging from 17% to 100%, still required medications to control their	1-	Systematic review	Various agents	41 cohort studies

	symptoms				
Brant 2006 [42]	Most patients continue to be troubled by, albeit improved, symptoms and experience difficulty in re-employment 2 yars after avoidance of exposure.	2+	Workforce-based follow-up	Enzymes (detergent industry)	35
Klusackova 2006 [43]	Symptoms of asthma and histamine hyperresponsiveness persisted in 86% and 61% of the patients, respectively, after avoidance of exposure.	3	Longitudinal follow-up	Various agents	37
Labrecque 2006 [10]	Nonspecific bronchial hyperresponsiveness was normalized in 11% of the patients and clinical remission occurred in 5%. No statistical difference for spirometry data and antiasthmatic medication use.	2-	Retrospective cohort	Isocyanates (compensated cases with various occupations)	79
Munoz 2008 [44]	Nonspecific bronchial hyperresponsiveness improved in 3 of those 7 patients who avoided exposure.	2-	Longitudinal follow-up	Persulfate salts (hairdressers)	7
Park 2006 [45]	Nonspecific bronchial hyperresponsiveness and lung function of patients can sometimes recover slowly through avoidance measures.	2-	Longitudinal follow-up	Reactive dyes	26
Park 2007 [46]	Not improvement in lung function, asthma severity (as determined by symptom and medication scores) and non-specific airway hyper-responsiveness to methacholine.	2-	Longitudinal follow-up	Reactive dyes	11
Pisati 2007 [28]	Airway sensitization to TDI and symptoms and functional airway abnormalities can persist for years after cessation of exposure.	2-	Longitudinal follow-up	Isocyanates (TDI) spray painters	25
Rachiotis 2007 [29]	The pooled rate of symptomatic recovery was 32% (95% CI: 26% to 38%). The pooled prevalence of persistent bronchial hyperresponsiveness was 73% (95% CI: 66% to 79%).	1-	Systematic review	Various agents	Assessment of symptomatic recovery in 39 studies; 1,681 patients and improvement in NSBHR in 28 studies; 695 patients.
Yacoub 2007 [47]	There was a significant improvement in airway responsiveness and inflammation 2	2-	Longitudinal follow-up	Various agents	40

	years after cessation of exposure.				
Ancillary question 4. "What is the effectiveness of reducing exposure through engineering control or relocation of affected workers"					
Beach 2005 [41]	Lack of data prevented conclusions about the effectiveness of reducing exposure	1-	Systematic review	Various agents	41 cohort studies
Bernstein 2003 [48]	No specific conclusion on reduction of exposure.	2-	Retrospective cohort	Latex	Reduction of exposure (20); avoidance of exposure (4)
Burge 1982 [49]	Nonspecific bronchial hyperresponsiveness returned to normal in only 1/8 workers with reduced exposure as compared with half of those who avoided exposure.		Longitudinal follow-up	Colophony (electronic solderers)	Reduction of exposure (8); avoidance of exposure (20)
Chan-Yeung 1987 [36]	All patients with continued exposure had respiratory symptoms and required medication while 40% recovered completely among those who avoided exposure.	2-	Longitudinal follow-up	Red cedar	Reduction of exposure (42); avoidance of exposure (136); persistence of exposure (54);
Merget 1999 [19]	For the majority of subjects with OA due to Pt salts transfer to low exposure areas as defined in this study may not be associated with a more unfavorable outcome as compared with complete removal from exposure sources.	2-	Cross-sectional retrospective survey	Platinum salts	Reduction of exposure (16); avoidance of exposure (58); persistence of exposure (9);
Moscato 1993 [21]	All patients who remained exposed were still symptomatic and required pharmacologic treatment.	2-	Longitudinal follow-up	Various agents	reduction of exposure (7); avoidance of exposure (18); persistence of exposure (n=4)
Munoz 2008 [44]	No improvement was observed in patients who continued to be exposed.	2-	Longitudinal follow-up	Persulfate salts (hairdressers)	Reduction of exposure (3); avoidance of exposure (7)
Paggiaro 1993 [50]	In most subjects, nonspecific bronchial hyperresponsiveness did not change. No specific conclusion pertaining to reduction of exposure.	2-	Longitudinal follow-up	Isocyanates (various occupations)	Reduction of exposure (7); avoidance of exposure (7)
Pisati 1993 [27]	Complete removal from exposure is the only effective way of preventing deterioration of asthma.	2-	Longitudinal follow-up	Isocyanates (TDI) with various occupations	Reduction of exposure (17); avoidance of exposure (43)
Rosenberg 1987 [39]	Patients who remained exposed to the	2-	Longitudinal	Isocyanates	Reduction of exposure

	same work conditions experienced unchanged or worse respiratory symptoms		follow-up	(various occupations)	(7); avoidance of exposure (20); persistence of exposure (4)
Vandenplas 2002 [51]	Reduction of exposure to latex should be considered a reasonably safe alternative that is associated with fewer socioeconomic consequences than removal from exposure.	2-	Longitudinal follow-up	Latex	Reduction of exposure (20); avoidance of exposure (16)
Ancillary question 5. "What is the effectiveness of reducing exposure through personal protective equipment?"					
Côté 1990 [6]	Indirect evidence supporting a beneficial effect of some personal respiratory devices. The proportion of subjects who used a twin-cartridge respirator was higher among the group with stable asthma (30%) than among the group with a deterioration of asthma (0%).	2-	Retrospective cohort	Red cedar dust	48
Kongerud 1991 [52]	Assessment: AH60 Airsteam helmet. Findings: Non significant reduction of symptom score in 10/17 subjects.; iimprovement in the mean peak expiratory flow values.	1-	Workplace exposure for 2 weeks; randomized controlled study but only workers with non severe disease.	Aluminium potroom work	19
Laoprasert 1998 [53]	Assessment: Laminar flow HEPA–filtered helmet. Findings: Decrease of symptom score and reduction of the decline in FEV1.	1+	Laboratory challenge study, randomize with placebo	Latex allergens (quantified exposure)	9
Muller-Wening 1998 [54]	Assessment: "Dustmaster" P2 filter (n=21), "Airstream helmet" P2 filter (n=4), "Airlite" P2 filter (n=1). Findings: Suppression of respiratory symptoms in 11/26 subjects, reduction in 15/26, but 4 required inhaled bronchodilator; reduction of the increase in airway resistance.	2+	Laboratory challenge study, non-randomized	Organic farm allergens	26
Slovak 1985 [55]	Assessment: Racal Airstream helmet respirator.	3	Workplace exposure for 6	Laboratory animal	10

	Findings: Suppression of respiratory symptoms and changes in peak expiratory flows in 6 of 8 asthmatic patients		weeks; uncontrolled intervention study.		
Taivainen 1998 [56]	Assessment: Powered dust respirator helmet with P2 filter. Findings. No effect on respiratory symptoms with the exception of sputum, rhinitis symptoms, corticosteroid treatment, and number of sick leaves; increase in morning peak expiratory flow values and reduced daily peak flow variability; no effect in subjects with severe asthma or irregular use of protective devices.	2+	Workplace exposure for 10 months; non-randomized, non-controlled trial.	Farming	24
Chapter 3: "What are the benefits of medical screening and surveillance?" (for more details including elaboration of references see [57])					
Agrup 1986 [58]	The prevalence of allergy to laboratory animals (LAA); On clinical investigation 30 were found to have symptoms and signs related to contact with animals, and allergy was confirmed by radioallergosorbent tests (RAST) and skin tests in 19.	2+	Cross sectional	Laboratory technicians and animal keepers	101
Agrup 1986 [58]	Out of 19 people with laboratory animal allergy symptoms & positive SPT for animals, 13 (68%) had a history of atopic dermatitis, rhinitis or asthma before **they** started work at the laboratory or reacted to one or more allergens in the standard battery, or both and were regarded as atopics. Of these 13 individuals 6 had a history of atopy and 12 had at least one positive SPT to the standard battery (animal test excluded). Atopic features were present in 3/11 (27%) people with animal related symptoms but with negative animal RAST & skin tests.	2-	Cross-sectional	Laboratory animals	124

	Of the 30 with no animal related symptoms, 6 (20%) had a history of atopic disease and / or a positive reaction to a standard test. Atopy (history of atopic diseases or positive SPT results with common allergens, or both) was more common among those with positive tests to laboratory animal allergens (p<0,001). Smoking habits did not differ significantly. *(The first symptoms appeared after a mean latent period of 2.3 years).*				
Amital 2004 [59]	A total of 151 cases of sudden and unexpected death occurred among enlisted military personnel during the period. Cardiac disorders caused 47% of deaths, followed by pulmonary causes (11%). Asthma was the most common risk factor having been previously recognized in 10 cases (6.7%). Eight of the 13 subjects with asthma died following an acute asthmatic attack. The frequency of subjects with asthma was found to be higher than that in the general age-adjusted population.	3	Case studies, retrospective	Military	151
Armentia 1990 [60]	One hundred thirty-nine bakers and pastry cooks were included in a prevalence study of IgE-mediated hypersensitivity to wheat flour demonstrated by skin tests, specific IgE to wheat flour (RAST), and inhalation challenge. From the sensitized workers, 30 asthmatic patients were selected. Twenty patients were treated with a standardized wheat flour extract, and ten with a placebo in a double-blind clinical trial. Before and after immunotherapy we performed tests in vivo (skin tests with wheat flour and methacholine tests), and in vitro (total IgE and specific IgE to wheat flour). Substantial	2-	Contr. clin. trial	Wheat/ baker	139

	prevalence of wheat flour allergy (25.17% of workers) were found, and a significant decrease (P less than .001) in hyperresponsiveness to methacholine, skin sensitivity (P = .002), and specific IgE (P less than .005) to wheat flour after 20 months of immunotherapy. There was also significant subjective improvement (P less than 0.001). The placebo group showed no changes in these variables.				
Auger 2002 [61]	Asthma from exposure to inhalation of isocyanates is an affection recognised under the title of workplace diseases within table no 62 in the General Regulations and no 43 in the Agricultural Regulations. If workplace induced asthma is the most frequent of the workplace respiratory illnesses with a frequency of 2 to 15% of the asthmatic population, 1 patient in 2 will only be the object of a declaration and 1 in 3 the objective of a survey by the administrative authorities. The frequency of isocyanate asthma is on average 16.4% amongst workplace asthmas (19.6% in the industrial environment and 1.5% in an agricultural environment); if this prevalence is dose-dependent according to Baur, 30% of patients exposed to weak doses of isocyanate (0.3% ppb according to White) develop asthmatic disease whilst Bernstein estimates as 5 to 10% the frequency of asthmatic disease per 100,000 persons who are exposed to isocyanates.	3	Nonanalytical study	Isocyanates	

Baur 2001 [62]	Methods In the present study we described five cases with workplace-related asthma and one case with extrinsic allergic alveolitis associated with pulmonary hemorrhage after NDI exposure.	3	Case studies	NDI, diisocyanate/ synthetic resin plant	6
Baur 2005 [63]	The literature review shows that airborne enzymes occurring in the general environment and in purified form in industrial production have a high allergenic potential to the airways, causing rhinitis, conjunctivitis and asthma. Cross-sectional studies demonstrate exposure-response relations for IgE-mediated sensitisation and airway disorders. Atopic individuals are more susceptible to enzyme allergy than non-atopic individuals. Skin prick testing and measurement of specific IgE antibodies have been shown to be useful diagnostic tools. There is also evidence for non-allergic airway inflammation by proteases.	2+	Cross-sectional	Enzymes	
Baur 1998 [64]	Study aimed to evaluate the frequency of work-related symptoms & the clinical relevance of sensitisation to allergens in 89 bakers participating in a screening study & 104 bakers filing a claim for compensation for bakers asthma. The correlation between the sensitisations to work-related allergens & present asthma case history & inhalative challenge test responses was significant. However, approximately 29% of the bakers with respiratory symptoms showed no sensitisation to these bakery allergens, whereas 32% of the sensitized bakers in the screening group had no workplace-related symptoms. Atopic status defined by skin prick test sensitisation to common allergens or elevated total IgE levels was	2-	Cross sectional	Flour & baking enzymes	193

	found to be a risk factor for the development of sensitisation to bakery allergens & respiratory symptoms. However, there is evidence for an increased frequency of elevated total IgE as the result of occupational allergen exposure because respective findings were observed in bakers without symptoms. Further methods are required to objectively assume irritative patho-mechanisms. Authors conclude that findings indicate the necessity for an improved primary prevention of exposure to inhalative noxae in bakeries.				
Baur 1982 [65]	Seventeen out of thirty-three workers who have been exposed to airborne papain at their place of work regularly developed asthmatic symptoms; Clinical symptoms and results of skin test, RAST and bronchial provocation test in thirty-three papain workers: evidence for strong immunogenic potency and clinically relevant 'proteolytic effects of airborne papain'. Only one case with pre-existing atopic diseases (allergic rhinitis). So it is not likely that that an atopic diathesis is a prerequisite for papain induced allergic reactions. As six subjects developed clinically relevant hypersensitivity to common allergens during the time of papain exposure, it is thought that airborne papain may constitute a triggering effect to further sensitisation. (Blood-stained nasal secretion, itching and flare reaction appearing on uncovered skin areas in heavily exposed subjects of whom three had negative and one weak positive SPT and RAST results, suggest a direct irritative effect and damage human tissue by high concentration of active proteinase papain.)	3	Case studies	Papain	33
Brant 2005 [66]	A cross-sectional survey was undertaken	2-	Cross-sectional	Flour, α-amylase,	239

	involving 239 (71%) employees from 20 different supermarket bakerles. The geometric mean dust exposure for bakers was 1.2 mg/m^3, a total of 37 (15%) employees also reported work-related chest symptoms. Serum IgE to flour was present in 24 (11%) employees and to fungal α-amylase in ine (4%) employees. The combination of work-related chest symptoms and specific IgE was found in six (9%) bakers, one (4%) manager and two (3%) assistants. Conclusions: This population of bakery workers has important levels of sensitisation and work-related respiratory symptoms, despite low levels of dust exposure.			supermarket	
Bryant 1995 [67]	Allergy to laboratory animals is an occupational hazard among laboratory animal handlers, especially for those who are atopic and sensitised to domestic animals, and may lead to the development of asthma. 228 Subjects were surveyed**.** Atopic subjects (positive SPT results with at least one common allergen) exposed to laboratory animals (particularly those sensitized to domestic animals) and animal attendants (with a high intensity of exposure to laboratory animals) had significantly higher frequencies of skin reactivity to laboratory animals and asthma than other subjects (77% and 30% respectively, among exposed atopic subjects and 84% and 33% respectively among animal attendants). LAA is an occupational hazard among laboratory animal handlers especially for those who are atopic and sensitised to domestic animals and may lead to the development of asthma. Screening for atopy and skin	2-	Cross-sectional study	Laboratory animals	228

	reactivity to lab animals before and during employment would enable those at risk to take precaution.				
Cockcroft 1981 [68]	An association significant at the 2% level was found between skin test atopic status & asthma from animal contact. Subjects with a previous history of asthma were not significantly more likely to develop symptoms from animal contact but were more likely to develop animal-related asthma. But nearly half of the subjects with animal-related asthma were non-atopic, two-thirds of the subjects with animal related-asthma had no previous history of asthma. The authors conclude that excluding atopic individuals will not solve the problem, & screening new entrants is unlikely to be successful in view of the long average exposure period before symptoms develop & the fact that skin reactivity to animal extracts is rarely present without symptoms.	2-	Cross-sectional	Laboratory animals	179
Codina 2000 [69]	56 (15.3%) out of 365 asthmatic/allergic rhinitis subjects showed positive SPT to soybean hulls but none out of 50 controls. There was a significant dose-response relationship in the first group (occupational > indirect > urban exposures). Monosensitization to soybean hulls was absent in all subjects. Asthmatic patients with a positive SPT to soybean hulls compared with those exclusively sensitized to mites, had a higher frequency of daily or weekly symptoms and a higher percent of glucocorticoid dependence.	2-	Cross-sectional	Soybean hulls	365
Cullinan 1994 [70]	344 employees exposed to flour in bakeries or mills in 7 sites were assessed by self completed questionnaire, & sensitisation measured by the response to skin prick	2+	Cross-sectional	Flour / bakers	344

	tests, were related to intensity of exposure both to total dust & to flour aeroallergen. Among 264 previously unexposed subjects, work-related symptoms (which started after first employment at site) were related to exposure intensity, especially when exposure was expressed in terms of flour aeroallergen. The relations with eye/nose & skin symptoms were independent of atopic status & cigarette smoking. Positive skin test responses to mixed flour & to α-amylase were also more frequent with increasing exposure intensity, although this was confounded by atopic status. There was only a weak association between symptoms & specific sensitisation.				
De Zotti 2000 [71]	Work-related respiratory symptoms are significantly associated with personal history of allergic disease (OR 5,8 95%CI 1,8-18,2). and skin sensitisation to wheat flour or a-amxlase (OR 4,3 95%CI 1,2-14,9). Atopy based on SPT was not related to respiratory symptoms over time (OR 1,1 95%CI 0,3-3,8). Similarly family atopy, atopy based on IgE concentration and positive RAST results for wheat flour were not associated with work-related respiratory symptoms. Authors conclude that personal history of allergic disease is a predisposing factor for the development of symptoms caused by exposure to wheat flour & may be a criterion of unsuitability for starting a career as a baker. Atopy based on the skin prick test is useful for identifying subjects with allergic disease, but should not be used to exclude nonsymptomatic atopic people from bakery work.	2+	Cohort	Flour / bakers	125
Gautrin 2001 [72]	28/417 apprentices satisfied the definition	2+	Prospective	Laboratory	417

	for 'probable occupational asthma', i.e., onset of immediate skin reactivity to > 1 occupational inhalant & > 3.2-fold decrease of PC20. The incidence of 'probable occupational asthma' was 2.7%. Baseline immediate skin reactivity to pets (rate ratio [RR] 4.1, 95% CI=1,6-10,8) & bronchial responsiveness (PC20 ≤ 32 versus PC20 > 32 mg/ ml) (RR = 2.5) were associated with an increased risk of probable occupational asthma; a lower FEV1 had an apparent, protective effect (RR = 0.58, 95%CI= 0,43 – 0,78). Authors conclude that apprentices in animal health show a high incidence of probable occupational asthma, & that preexposure airway calibre & responsiveness as well as sensitisation to pets are associated with an increased risk. After multivariant analysis, atopy increases not significantly the likehood of developing OA. This study adds some evidence that asthma is not a risk factor for the incidence of 'probable occupational asthma, & also suggests that having a high FEV1 does not preclude the development of 'probable occupational asthma'.		cohort study	animals	
Gautrin 2000 [73]	Prospetive cohort study including 769 apprentices (animal health technology: 417, pastry-making: 230, dental hygiene: 122). Atopy (> positive SPT results with common inhalants), nasal and respiratory symptoms in the pollen season (and duration of exposure to rodents) were the most significant predictors for sensitisation in the animal health program. Rhinitis symptoms on the contact pets before starting apprenticeship were also associated with incidence of sensitisation in the case of animal health apprentices. Hay fever on	2+	Prospetive cohort	Laboratory animals	169

	entry into program was strongly associated with the risk of sensitisation to flour in the pastry-making program. Reporting asthma on the entry in the dental-hygiene program is related to the probability of developing specific sensitisation. The apprenticeship in the animal health technology carries a greater risk of developing specific sensitisation than do apprenticeships in pastry-making and dental hygiene. A non-negligible number of new cases of sensitization ton non-WR occupational antigens was found in all three programmes.				
Gautrin 2001 [74]	Study describes the time-course of the incidence of work-related symptoms, skin reactivity and occupational rhino-conjunctivitis (RC), and occupational asthma; & assesses the predictive value of skin testing & RC symptoms in apprentices exposed to laboratory animals. The positive predictive values (PPVs) of skin reactivity to work-related allergens for the development of work-related RC & respiratory symptoms were 30% & 9.0%, respectively, while the PPV of work-related RC for the development of occupational asthma was 11.4%. The PPV of WR respiratory symptoms for the development of OA was 25%. Skin reactivity to work-related allergens & rhino-conjunctivitis symptoms have low positive predictive values. The data suggest that assessment of skin reactivity and RC symptoms should still be considered in the context of screening programmes. Sensitization, symptoms and diseases occur maximally in the first 2–3 yrs after starting exposure to laboratory animals.	2+	Prospective cohort (same collective as Gautrin 2001 [72]	Laboratory animals, pastry making, dental hygiene technology	417

Gautrin 2008 [75]	Sensitization to mites and NSBHR at baseline are significantly associated to new sensitization to work-related allergens. Physician diagnosed asthma and NSBHR at start are significantly associated with the incidence of chest symptoms. Sensitisation to pets at baseline and respiratory symptoms at the end at apprenticeship are significantly associated with an increase in BHR. The changes in frequency (incidence and remission) of sensitisation and diseases are unlikely to be due to frequently incriminated host factors such as atopy or smoking.	2+	Cohort	Laboratory animals	408
Gordon 1997 [76]	A questionnaire was issued to 362 flour-exposed workers in a large bakery. The respiratory screening questionnaire identified 68 workers with respiratory symptoms. Of these, 21 proceeded to full assessment. A diagnosis of asthma was made in 5 cases, one of which was bakers' asthma. In addition, 11 workers not reporting any symptoms by questionnaire were referred to clinic & five were diagnosed as having asthma. Authors conclude that screening questionnaires may lead to an underestimate of the prevalence of asthmatic symptoms & as such should not be used alone in workplace screening. In terms of sensitivity the questionnaire used in this study missed as least as many cases as it detected.	2-	Cross-sectional	Flour / bakers	362
Grammer 1993 [77]	The objective of the study was to determine the clinical and immunologic status of trimellitic anhydride (TMA) workers who have had immunologic lung diseases and who have been moved to lower exposure jobs. Twenty-nine consecutive workers with TMA-induced immunologic lung diseases	2-	cohort, retrospective	TMA	29

	who had been moved to low exposure jobs for more than 1 yr were studied retrospectively. Pulmonary symptoms were obtained by physician-administered questionnaire. Immunologic studies were performed using radioimmunoassay. Spirometry and chest film were obtained. Workers with late asthma (LA) (n=3), late respiratory systemic syndrome (LRSS) (n=8), or both LRSS and asthma rhinitis (A/R) (n=6) had improved symptoms, improved pulmonary functions, and lower total antibody against TM-HSA				
Houba 1996 [78]	In this cross-sectional study, sensitization to occupational allergens and work-related symptoms were studied in 178 bakery workers and related to allergen exposure. α-amylase allergen concentrations were measured in personal dust samples. Of all workers 25% had one or more work-related symptoms. As much as 9 %of the bakery workers showed a positive skin prick test reaction to fungal amylase, and in 8% amylase-specific IgE was demonstrated. Alpha-amylase exposure and atopy appeared to be the most important determinants of skin sensitization, with prevalence ratios for atopy of 20.8 and for medium and high α-amylase exposure groups of 8.6 and 15.9 respectively. Furthermore, a positive association was found between positive skin prick tests to α-amylase and work-related respiratory symptoms. There is a strong and positive relationship between α-amylase allergen exposure levels in bakeries and specific sensitization in bakery workers.	2+	Cross-sectional	α-amylase (bakers)	178
Juniper 1984 [79]	Atopics were significantly more likely to suffer from enzyme asthma than non-	2-	Cohort	Alcalase (enzyme)	55

	atopics. The authors conclude that subjects with previous chest disease should not be exposed to Alcalase or similar occupational allergens, but that exclusion of asymptomatic atopics from this type of work is probably not justified. 62/1642 subjects experienced enzyme asthma with higher incidence in atopics.				
Kim 1999 [80]	The prevalence of asthma was higher in subjects with positive SPT results or high serum specific IgE antibodys to citrus red mite than in those without skin response or serum specific IgE (p<0,05, respectively). In this study, sensitization to citrus red mite (CRM) and the prevalence of CRM-sensitive asthma and rhinitis were significantly higher in farmers with positive SPT results to other inhalant allergens than in those without. This finding suggests 1. that atopy may be a risk factor for sensitization to CRM and for the development of asthma and rhinitis caused by CRM. 2. a +SPT to house dust mites may reflect cross-reactivity.	2-	Cross-sectional	Citrus red mite	181
Kongerud 1991 [81]	The influence of occupational work exposure and host factors on the incidence of dyspnea and wheezing as reported in questionnaires was examined in 1301 new employees in aluminium electrolytic potrooms. Childhood allergy was not significantly associated to these outcomes. A family history of asthma was associated with the reporting of work related asthmatic symptoms (RR=1.58) although the estimate did not reach the level of statistical significance, but was found to be significant in a previous study (OR=1.64). Exposure to dust or gases in previous jobs was significantly related to appearance of	3+	Cohort	Aluminium potroom workers	1301

	symptoms. Increased risk with increasing amount of tobacco smoking and total fluoride exposure was found. A dose response gradient was seen for both variables. No significant differences in FEV1 and FVC were observed between symptomatic and asymptomatic subjects. In this study the increased risk from allergy to develop asthmatic symptoms was small (OR=1.35), unsignificant and in accordance with a previous study of the same group (OR=1.38). Exclusion of allergic people from potroom work would probably have no effect on the incidence of asthmatic symptoms. (CAVE: Diagnosis only base on self-reported symptoms.) Flouride exposure and smoking are the major risk factors for the development of dyspnea and wheezing.				
Kongerud 1990 [82]	1. Family history of asthma is sign. related to dyspnea (OR 1,53 95%CI 1,14 - 2,06) and work-related asthmatic symtoms (OR 1,64 95%CI 1,08 - 2,49) 2. Allergy (history of hayfever or atopic eczema) provided no sign. risk for resp symptoms and was neg. correlated with airflow limitation.	2+	Cross-sectional	Aluminium potroom workers	1679
Kronqvist 1999 [83]	BACKGROUND: Earlier studies from several countries have shown that IgE-mediated allergy in rural populations is of considerable importance and that storage mites are dominant allergens. OBJECTIVE: In an epidemiological follow-up study among farmers on the island of Gotland, Sweden in 1996 we wished to investigate the prevalence of respiratory allergy and to find out whether storage mites are still important allergens in a farming environment. METHODS: A	2++	Epidemiological follow-up	Storage mite/ Dairy farmers	1015

	questionnaire concerning airway symptoms, social and working conditions and smoking habits was distributed to all Gotland farmers aged 15-65 years and was completed by 1577 (86.7%), of whom 1015 were dairy farmers. Based on the answers, 500 dairy farmers were invited to undergo a medical examination which included a skin-prick test (SPT) and blood sampling for RAST analyses. Prevalence figures (symptoms, RAST and SPT) given for the whole population (n = 1015) were based on the investigation of the 461 farmers who took part in the examination. RESULTS: Immediate onset hypersensitivity was present in 41.7% of the 1015 farmers studied, which is almost the same figure as in 1984 (40.0%). The prevalence of asthma had increased significantly during the previous 12 years (5.3% vs 9.8%), as had asthma in combination with rhinoconjunctivitis (3.7% vs 7.0%). Rhinoconjunctivitis, on the other hand, had not changed significantly (36.5% vs 33.1%) and remained one of the most common symptoms. The prevalence of storage mite allergy in the farming population in 1996 was 6.5% and constituted an important cause of allergic symptoms. CONCLUSION: Over 12 years, Gotland dairy farmers have developed significantly more respiratory symptoms from the lower airways, although the proportion with atopy is				

	unchanged. Storage mites are still dominant allergens for developing allergic disease.				
Kruize 1997 [84]	Aimed to study the role of exposure, atopy & smoking in the development of LAA. Study showed that both non-atopic & atopic people seemed to have an increased risk related to exposure intensity when exposed to laboratory animal allergens. Atopic people developed LAA earlier & in more severe forms (asthma) than non-atopics (13% v 6%). An increased RR was found for atopic people to develop LAA (RR=4,2 (1,5 – 11,3), p<0,05). Authors conclude that exposure & atopy are significant predictors of LAA & that the risk of developing LAA remained present for a much longer period (>3 years) than considered before. Sex, smoking and age were no risk factors.	2+	Cohort	Laboratory animals	99
Larbanois 2002 [85]	Subjects (n=157) who were being investigated for work-related asthma, were surveyed. Of these 86 had OA, ascertained by a positive specific inhalation challenge (SIC), and 71 subjects had a negative SIC response. After a median interval of 43 months (range 12–85 months), the subjects were interviewed to collect information on employment status, income changes, and asthma-related work disability. Rates of work disruption and income loss at follow-up were similar in subjects with negative SIC (46% and 59%, respectively) and in those with OA (38% and 62%). The median loss as a percentage of initial income was 23% in subjects with negative SIC and 22% in subjects with OA. Asthma-related work disability, defined as any job change or	2-	Cohort	Various	157

	work loss due to asthma, was slightly more common in subjects with OA (72%) than in those with negative SIC (54%). This study shows that, even in the absence of demonstrable occupational asthma, work-related asthma symptoms are associated with considerable socioeconomic consequences.				
Mackie 2008 [86]	To assess the efficacy of a UK-wide health surveillance programme provided to the motor vehicle repair industry. Analysis of respiratory questionnaire and spirometry results during the period 1995–2000 and more detailed assessment of the outcome of cases suggestive of OA between 1998 and 2000. Approximately 3,700 employees underwent health surveillance each year. As a result, a number (27%) required further assessment; information on 92 employees who were referred to their general practitioner (GP) for further assessment was examined. Half of these employees subsequently failed to see their GP and of those referred to a specialist only 63% attended that appointment. Of the 20 employees who did see a specialist, nine (45%) were subsequently diagnosed as having OA due to isocyanates, indicating a mean annual incidence rate of 0.79 per 1,000 workers identified by surveillance. A year after identification, five of the diagnosed employees were still working in the same job.	2-	Cohort, retrospective	Diisocyanates / vehicle repair industry	92
Mapp 1986 [87]	Six workers with TDI induced OA were studied. Methacholin challenge was within normal limits before TDI-Inhalation, but went into asthmatic range after TDI challenge. Isolated neg. Methacholin test	3	Case series	Isocyanates / TDI	6

	cannot be used to exclude sensitization. Since variable airflow obstruction and BHR are the main characteristics of asthma, serial measurements of BHR and PEF may be helpful in providing data on sensitized workers and in following workers with OA. BHR may be a helpful screening test in the pre-employment visit.				
Meadway 1980 [88]	Seven workers using an epoxy adhesive cured with pyromellitic dianhydride were studied. There is no clear relationship between smoking habits, atopic status or skin rashes with resin and a fall in FEV1. There is no simple way to identify those at risk of developing wheeze. Where sensitization occurs a simple questionnaire would provide a screening method.	3	Case series	Epoxy adhesives	7
Meijer 2002 [89]	High and low risk categories for work related sensitisation can be distinguished from simple questionnaire data and SPT results. The method can easily be applied in occupational medical practice and may markedly increase the efficiency of occupational health surveillance in laboratory animal workers as well as other workers exposed to HMW allergens.	2+(+)	Cohort	Laboratory animal workers	551
Meijer 2010 [90]	Performance of the model was evaluated in 674 randomly selected bakers who participated in the medical surveillance program and in the validation study. Clinical investigations were evaluated in the firstly referred 73 bakers. This prediction based stratification procedure appeared effective in detecting work-related allergy among bakers and can accurately be used for periodic examination, especially in small enterprises where delivery of adequate care is difficult. The approach may contribute to cost	2-	Cross sectional survey	Wheat / bakers	5325

	reduction.				
Meijer 2004 [91]	Diagnostic and prognostic prediction models to detect and predict occupational allergic diseases; The risk of (future) sensitisation and the severity of laboratory animal allergy can be predicted accurately with diagnostic and prognostic prediction models based on questionnaire items. Workers with an increased risk of future sensitisation also showed serious allergic symptoms at follow up. Workers with a low risk have a low risk of becoming diseased in the future.	2+	Model/cohort	Lab animal workers	351
Meijer 2002 [91]	Prediction models based on questionnaires can be used effectively. The diagnostic model derived from questionnaire items included gender**,** wheeze, allergic symptoms during work, allergic symptoms during last year, and work for more than 20h / week with rats as independent predictors for outcome (sensitisation). Splitting a population of laboratory animal workers into a group with high and a low probability of sensitisation, offers an appropriate and practical first diagnostic step (sensitivity 71%, specificity 69%, accuracy 69%) and increases the efficiency of medical investigations by occupational professionals. Accuracy can be improved by additional test (specific IgE or SPT for common allergens). Additional testing recommended in the high risk group. Prediction models based on standardised questionnaire extended with work related questions can be used to detect and predict accurately the risk of sensitisation to HMW workplace allergens and the severity of allergic diseases. A strategy to initially divide the population into	2+	Review-like study with data derived model	Laboratory animals	586

	a group with high and low sensitisation probability by applying a diagnostic model can markly The developed strategy has been shown to be reliable by identifying relatively sever allergic diseases absenteeism, and doctor's visit in workers with high sensitisation probability. Workers with a high risk of future sensitisation presented serious allergic symptoms at follow up. Workers with a low risk of future sensitisation have a low risk of becoming diseased in the future.				
Merget 1988 [92]	Anamnestic & immunological data of platinum refinery workers were compared (group A: workers with work-related symptoms (8); group B: workers with symptoms not clearly work-related (9); group C: asymptomatic workers (13) & controls (group D: atopics (10); group E: non-atopics (16)). Exposure to platinum salt was higher in group A than in groups B or C. All subjects of group A & 3 workers of group B, but none of the workers of the other groups, showed a positive cutaneous reaction to platinum salts. Total serum IgE was higher in groups A & D than other groups, however platinum salt-specific IgE was higher in group A. Histamine release with platinum salts was found in all groups & was highest in atopic controls. History of pre-exposure allergic diseases was more frequently in a group with work related symptoms (n.s.). It is not possible to predict weather a subject will acquire platinum salt allergy by means of anamnestic data. Authors conclude that neither histamine release from basophils with platinum salts, nor RAST for the detection of platinum salt-specific IgE are helpful in the diagnosis of	2-	Cross-sectional	Platinum salts	27

	platinum salt allergy.				
Merget 2001 [93]	Objective: We sought to assess the effectiveness of a medical surveillance program in workers with exposure to platinum salts. Methods: A nested case-control study was performed in 14 workers of a catalyst production plant whose skin prick test (SPT) responses to platinum salt converted from negative to positive during a 5-year prospective cohort study with yearly medical examinations and 42 matched control subjects from the plant who did not experience SPT response conversion. With the exception of 2 subjects, the workers showing SPT response conversion were removed completely from exposure sources and followed for up to 42 months. Results: Work-related new symptoms were reported by 9 of the 14 subjects, and new symptoms without relation to work were reported by 3 subjects at the time of SPT response conversion. Symptoms were not accompanied by a change in FEV1 or bronchial responsiveness to histamine. Symptoms resolved after transferral, but occasional shortness of breath or wheeze persisted in 4 subjects. SPT reactions decreased or became negative in all workers after complete removal but remained unchanged in a craftsman with ongoing occasional exposure to contaminated materials. Conclusion: Although no randomized intervention was performed, this study proves the effectiveness of a medical surveillance program for the prevention of occupational asthma caused by platinum salts.	2++	Nested case-control, prospective	Platinum salts/catalyst production plant	56

Monsó 2004 [94]	A sample of participants in the European farmers' study was selected for a cross-sectional study assessing lung function and air contaminants. COPD was found in 18 of 105 farmers. Dust and endotoxin showed a dose-response relationship with COPD, with the highest prevalence of COPD in subjects with high dust and endotoxin exposure. This association was statistically significant for dust in the multivariate analysis.	2-	Cross-sectional	Farming dust, endotoxin	105
Newill 1986 [95]	The use of screening criteria as determinants for hiring persons to work with laboratory animals is unwarranted because of the dearth of reliable estimates of the strength of association between the screening criteria and LAA.	2-	Data analysis	Laboratory animals	
Nielsen 2001 [96]	154 exposed workers and 57 referents where studied. Air levels where low and associated with the concentrations of metabolites in urine. Furthermore, for the exposed workers, there were high prevalences of sensitization which correlated with the exposure. Neither atopy nor smoking increased this risk significantly. Furthermore, work-related symptoms were more prevalent among the exposed workers than among the referents and they were related to the exposure in the highest group and the specific IgE levels.	2-	Cross-sectional (heavy exposure was excluded)	Anhydrides	154
Park 2001 [97]	Study aimed to evaluate the clinical validation of skin prick tests (SPT) & measurement of specific IgE to vinyl sulphone reactive dyes by ELISA. 42 patients with occupational asthma from reactive dyes, 93 asymptomatic factory workers & 16 unexposed controls were enrolled. None of the unexposed controls	2-	Case-control	Vinyl sulphone active dyes	42

	had a positive response to SPTs. The sensitivity (76.2% v 53.7%), specificity (91.4% v 86.0%), positive predictive value (80.0% v 62.9%), & negative predictive value (89.5% v 80.8%) of SPTs were higher than those of ELISAs. Sensitivity (83,3%) and NPV (91,7%) of combined test are even higher. In 4 patients with occupational asthma from reactive dyes & 8 control subjects exposed to reactive dye, IgE specific to reactive dye conjugated to human serum albumin was detected with ELISA even though they showed negative skin reactivity. 6 patients completely avoided the reactive dye for a mean (SD) 27.8 (10.3) months, IgE specific to reactive dyes decreased in all six patients during this time. Authors conclude that both SPTs & detection of IgE specific to reactive dye in serum samples could be valuable for screening, diagnosis, & monitoring occupational asthma resulting from exposure to reactive dyes. These two tests would complement each other. Atopy (pos. SPT for common allergens) higher in OA group (52,4% vs. 32,3% $p<0,05$).				
Peretz 2005 [98]	About 270 Dutch wheat flour exposed bakers, millers and bakery-ingredient goodproducers were investigated for sensitization to wheat and common allergens. Further, 520 inhalable dust and wheat-allergen measurements were done. The relation for the whole study population was best described as quadratic, and the probability of sensitization increased with exposure up to c. 2.7 mg/m^3 for inhalable dust and c 25.7 µg EQ/m^3 for wheat allergens. The risk decreased at higher exposures. Atopy and sector of industry	2+	Cross-sectional	Flour	270

	modified the sensitization risk significantly in all the analyses. Conclusions: Exposure-response relationships for allergens may be nonlinear and differ between industries. A threshold is not indicated.				
Portengen 2005 [99]	162 pig farmers underwent a cross-sectional case-control study. Data on endotoxin exposure and serum-IgE levels were available. IgE to one or more common allergens was detected in sera from 28 (17%) farmers. A strong inverse relationship was found between endotoxin and sensitization to common allergens for exposures of 75 ng/m^3 or less, with an odds ratio of 0.03 (95% CI, 0.0-0.34) for a 2-fold increase in endotoxin. For endotoxin exposure of greater than 75 ng/m^3, the association was weak. No association was found between endotoxin exposure and total IgE levels. Endotoxin was associated with increased airway responsiveness to histamine and lower lung function in sensitized farmers, without evidence of a nonlinear relationship. Conclusions: Endotoxin or related exposures might protect from sensitization, even in an adult working population, but is a risk factor for increased airway responsiveness and low lung function.	2+	Cross-sectional	Pig farmers	162
Redlich 2001 [100, 101]	Objectives We have initiated a cross-sectional field epidemiologic study, Survey of Painters and Repairers of Auto bodies by Yale (SPRAY), to characterize the effects of diisocyanate exposures on actively employed auto body shop workers. Methods and Results We present here questionnaire, physiologic, immunologic, and exposure data on 75 subjects enrolled in the study. No overt cases of clinically	2+	Cross-sectional field epidemiologic study	Autorepair/ HDI isoc	75

	apparent diisocyanate asthma were identifed based on spirometry, methacholine challenge, peak flows, and symptoms.				
Redlich 2002 [101]	Objectives A 1-year follow-up was undertaken as an adjunct to the cross-sectional SPRAY study (Survey of Painters & Repairers of Auto bodies by Yale) to investigate the effects of HDI on auto body shop workers over time and whether or not the healthy worker effect may exist in this industry. Conclusions The differences in workers who stayed at their shop compared to those who left, combined with the low asthma prevalence and high job turnover rate, all suggest that a healthy worker effect may exist in the auto body industry, and may in part account for the low prevalence of asthma noted in SPRAY and other cross-sectional studies of diisocyante workers.	2+	Cross-sectional, follow-up	LMW/isoc HDI/ Autorepair	48
Renstrom 1994 [102]	In a prospective study of laboratory technicians, selected indicators of allergy & atopy were studied in an attempt to determine predictors of laboratory animal allergy (LAA). Total IgE was sign. higher before exposure in subjects who developed symptoms [and sensitisation] than in non symptomatic subjects, total IgE > 100 kU/l PPV=0.44 [PPV =0.33]. Nasal symptoms before exposure more frequent in sensitised subjects (PPV = 0.44). PPV of family allergy was 0.17. From results it does not seem likely that refusing to employ atopic subjects in animal work will prevent the development of LAA. Preventing atopic subjects from animal work would only have reduced the 9	2+	Cohort	Laboratory animals	225

	sensitised and/or symptomatic subjects to 7. Preventing subjects with total IgE levels >100 kU/l from working with animals would have reduced the number of subjects developing LAA to 2 instead of 9. On the other hand, 8 non-reactive subjects (after this study) would also have been excluded from such work.				
Roberts 2004 [103]	The prevalence of asthma among working adults continues to rise each year. The California Department of Health Services conducts surveillance of work related asthma (WRA) to classify each work related exposure using Doctor's First Reports of Occupational Illness and Injury (DFRs). Using a cross-sectional, descriptive, comparative design, additional interviews were conducted and medical records were reviewed to explore workers' and providers' perceptions of follow up care. Two cohorts were compared: workers with WRA who belonged to a large, single HMO (n = 79) and workers with WRA who underwent follow up outside this HMO (n = 76). The interview asked about providers seen, tests ordered, and the impact of asthma on work. The HMO clients were significantly more likely than the non-HMO clients to see occupational medicine specialists (p = .004) and have pulmonary function testing (p = .049) during initial treatment. Twenty-four percent of clients currently working reported missed workdays caused by asthma in the past 6 months. The findings indicate management of WRA varies by health care system in California.		Cross-sectional		155
Robertson 2007 [104]	Investigation of an outbreak (12 workers) of EAA in the UK between 12/2003 and	2+	Cross-sectional	Metal working fluid / car	808

	05/204. Half of the asthma cases (74, defined by serial peak flow records) had asthma before 2003. Exposure related diagnosis (OA, EAA): 3,5 fold greater risk at largest common sump.			engineers	
Schumacher 1981 [105]	121 exposed and 50 unexposed subjects were studied by questionnaire and SPT with 7 common aeroallergens and allergens from mice. In subjects with seasonal allergic rhinitis or positive SPT results with common aeroallergens, work-related nasal symptoms and mouse-specific positive SPT and IgE were more prevalent. This suggests a predisposition to mouse allergy was related to the coexistence of atopic diathesis. Work-related eye or chest symptoms are not significantly associated with seasonal rhinitis. WR Symptoms from mice or +SPT to mouse AGs did not correlate sign. with a family history of allergic rhinitis, asthma or eczema A negative association between the incidence of HLA-DRW6 and SPT+ to mice antigens suggests a possibility of genetic influence on susceptibility to mouse allergy. Screening of prospective employees in mouse laboratories by questionnaires could be improved by use of pollen SPT in the pre-employment assessment to minimize need for compensation for occupational disability. But many pollen SPT+ subjects did not develop symptoms, indicating that pollen SPT for screening purpose could preclude employment of a person who could work among mice without becoming sensitized.	2-	Cross-sectional	Laboratory animals	171
Sjostedt 1989 [106]	LAA asthmatics have an increased frequency of family history of allergy	2+	Cohort	Laboratory animals	101

	(RR=3,8; PPV=0,27) and a positive SPT results with common non-animal allergens (RR=15; PPV 0,60). All persons with marked positive SPT to environmental allergens have developed animal positive LAA asthma. 56% LAA asthama cases IgE > 100 kU/L Pre-employment screening: family history of allergy and pos SPT.				
Skjold 2008 [107]	114 baker apprentices were surveyed over 20 month period. An increased risk of asthma like symptoms was found in atopics and females. In subjects with new onset respiratory symptoms an increase of BHR from baseline was observed. FEV1 and FVC did not change during follow up period. No relationship between new sensitisation and new symptoms. The mechanism by which symptoms arose was perceived to reflect the development of an inflammation rather than the production of a specific IgE pathway, as sensitization to WR allergens was rarely observed. Hence respiratory symptoms and allergy may also develop through separate pathways.	2+	Cohort	Bakers	114
Slovak 1987 [108]	Helmet respirator would appear to be a valuable adjunct in the management of occupational asthma in those that opt to remain in exposure. However, they should be monitored carefully & regularly to ensure that their respiratory function has not deteriorated. Objective evidence of good protection was obtained in 6/8 asthmatics.	2-	Case series	Laboratory animals	146
Smit 2008 [109]	Occupational endotoxin exposure in adulthood is associated with asthma-like symptoms (wheezing, shortness of breath, daily cough) but reduced prevalence of hay fever	2-	Cross-sectional	Endotoxine	877
Smith 1999 [110]	The objective of this study was to describe	2+	Cross-sectional,	Wheat, amylase/	3,450

	the incidence of allergic respiratory disease and its outcome in terms of symptoms and jobs,.across different flour-using industries. It uses the findings of a health surveillance programme in a large food organization over a five-year period. The population under surveillance consisted of 3,450 employees with exposure to ingredient dusts, of whom 400 were in flour milling, 1,650 in bread baking, 550 in cake baking and 850 in other flour-using operations. A total of 66 employees with either asthma or rhinitis symptoms attributable to sensitization to allergens in the workplace were identified. The majority of these (48/66) had become symptomatic prior to the commencement of the hearth surveillance programme in 1993. The incidence rates (per million employees per year) for those who developed symptoms between 1993 and 1997 were 550 for flour milling, 1,940 for bread baking, 0 for cake baking and 235 for other flour-using operations. The agent believed to be responsible for symptoms was most commonly grain dust in flour millers and fungal amytase in bread bakers. Wheat flour appeared to have a weaker sensitizing potential than these other two substances. In terms of outcome, at follow-up 18% of symptomatically sensitized employees had left the company. Two of the ex-employees retired through ill health due to occupational asthma. Of those still in employment, 63% described an improvement in symptoms, 32% were unchanged and 4% were worse than when first diagnosed. Over half the cases still in employment were continuing to work in the		follow-up; health surveillance programme	millers and bakers	

	same job as at the time of diagnosis.				
Suarthana 2005 [111]	Dutch laboratory animal (LA) workers and bakers using logistic regression analysis. Validity was assessed internally by bootstrapping procedure, and externally in British LA workers. It is possible to develop a generic model for sensitization to occupational HMW allergens. However, the weighing of predictors differs across specific work environments	(2+)	Modeling	Bakers, laboratory animals workers,	427, 936
Suarthana 2008 [112]	The baseline value of a questionnaire used alone or in combination with SPT to common allergens and/or BHR testing with Methacholin in predicting the occurrence of sensitization to laboratory animal (LA) allergens and respiratory symptoms was assessed. Questionnaire is a good tool to predict the incidence of occupational sensitization and symptoms. Additional test improve the specificity of the prediction for LA sensitization.	?	Cross-sectional	Laboratory animals	314
Taiwo 2006 [113]	Asthma occurs excessively among potroom workers and if so, delineate dose–response relationships for possible causal risk factors. The prevalence of asthma in our study population at baseline was 6.9%. The annual incidence of asthma observed in potroom workers in this study population was 1.17%. Potroom asthma appears to occur at the studied U.S. aluminum smelters at doses within regulatory guidelines.	2+	Cross-sectional	Potroom / fluoride	14,002
Tarlo 1997 [114]	Within this database, levels of isocyanate concentrations measured were compared at 20 case companies with 203 non-case companies, based on air samples collected during the 4-year period during which occupational asthma claims arose. The	2-	Database and case statistic analyses	Isocyanates	6,308

	proportion of case companies that were ever recorded as having a measured ambient isocyanate concentration of ≥ 0.005 ppm was greater than that for noncase companies, for TDI users (43% vs 22%), and for MDI users (40% vs 27%). This reached conventional significance when combined across companies and isocyanate types.				
Tarlo 1997 [115]	203 students and staff members completed the questionnaire. 5 percent reported asthma symptoms on exposure to rubber products, 13% reported symptoms of rhinitis or conjunctivitis and 17% reported pruritus or urticaria within minutes of exposure to rubber. Among the students tested, there were increasing percentages of positive skin test responses to latex with increasing years of study. Positive responses were seen as early as year 3 in students. Positive skin prick test responses to latex were related to a personal history of atopy ($p = 0.005$), positive skin prick test responses to common allergens ($p < 0.005$), latex-attributed immediate pruritus or urticaria ($p < 0.05$), rhinoconjunctivitis ($p < 0.001$), and asthma symptoms ($p < 0.001$). Conclusion: Dental school students and faculty are at high risk for latex sensitization…	2-	Cross-sectional	Latex (dental students)	203
Tarlo 2001 [116]	This study assesses the effects of intervention to reduce NRL allergy in an Ontario teaching hospital with approximately 8,000 employees. A retrospective review assessed annual numbers of employees visiting the occupational health clinic, allergy clinic, or both for manifestations of NRL allergy compared with the timing of introduction of	2+	Cohort, retrospective	Latex / health care workers	8,000

	intervention strategies, such as worker education, voluntary medical surveillance, and hospital conversion to low-protein, powder-free NRL gloves. The number of workers identified with NRL allergy rose annually, from 1 in 1988 to 6 in 1993. When worker education and voluntary medical surveillance were introduced in 1994, a further 25 workers were identified. Nonsterile gloves were changed to low–protein, powder-free NRL gloves in 1995: Diagnoses fell to 8 workers that year, and 2 of the 3 nurses who had been off work because of asthma-anaphylaxis were able to return to work with personal avoidance of NRL products. With a change to lower protein, powder-free NRL sterile gloves in 1997, allergy diagnoses fell to 3, and only 1 new case was identified subsequently up to May 1999. No increased glove costs were incurred as a result of consolidated glove purchases. This program to reduce NRL allergy in employees was effectively achieved without additional glove costs while reducing expenses from time off work and workers' compensation claims.				
Tarlo 2002 [117]	The introduction of a medical surveillance program (in Ontario, Canada) in 1983 was followed by retrospective assessments to determine benefits. Between 1980 and 1993, the proportion of all accepted compensation claims for OA that were attributed to diisocyanates, classified by year of symptom onset in the province with the program, rose to 64 percent by 1988, then fell significantly down to 29 percent in 1992 and 35 percent in 1993. Among those with diisocyanate-induced OA, an earlier diagnosis and a trend to	2+	Case series, retrospective	Isocyanates	136

	better outcome was found in workers from companies that were identified to be in compliance with surveillance measures.				
Venables 1985	An outbreak of occupational asthma, of unknown cause and extent, was detected in a steel coating plant. In 1979 a cross-sectional study which defined occupational asthma in terms of respiratory symptoms detected 21 people with suggestive symptoms among the 221 studied.	2-	Cross-sectional	Steel coating / isocyanates	221
Venables 1988 [118]	The correlation of symptoms suggestive of occupational asthma, symptoms suggestive of any occupational allergy, skin wheals to animal urine extracts, & serum RAST tests with urine extracts with atopy or smoking was investigated. Pooled data showed an association between smoking & all indices except RAST; the association was significant for symptoms of occupational asthma. One of the three surveys consistently showed a stronger association of allergy indices with smoking than with atopy (positive SPT results with non-animal aeroallergens). The ratio of prevalence in atopics compared with the group of non-atopics was 2,6 (p=0,023) for LAA chest symptoms, 2,1 (p<0,001) for skin weal to animal urine extract and 2,2 (p<0,001) for RAST+ to animal urine extract. No significant association was found between atopy and any LAA symtomy (ratio=1,3; p=0,332).	2+	Survey of 3 cross-sectional studies	Laboratory animals	296
Venables 1988 [118]	Survey was carried out on 138 workers exposed to laboratory animals. 44% had symptoms in a self-completed questionnaire that were consistent with laboratory animal allergy (LAA) of whom 11% had chest symptoms. LAA chest symptoms were almost 5 times more	3	Cross-sectional	Laboratory animals	158

	common in atopic (positive SPT result with non-animal aeroallergens) than non-atopic subjects. Positive SPT results with animal urine extracts was associated with LAA chest symtoms and atopy. Atopy was not associated with LAA eye, nose or skin symptoms when present without chest symptoms and only weakly associated with positive RAST results when present without a positive SPT results. As atopy is common in the general population it is difficult to justify excluding atopic subjects from employment with animals, but atopic subjects who develop positive skin tests to animal allergens may be at particular risk of chest symptoms & could be identified during employment & advised on risk. Regular screening at least provides useful information on the scale of the LAA within an organisation & in conjunction with occupational histories may point to particular working areas or practices that should be modified.				
Wild 2005 [120]	The authors used a mathematical simulation model of isocyanate asthma to compare annual surveillance to passive case finding. Outcome measures included symptom free days (SFD), quality adjusted life years (QALY), direct costs, productivity losses, and incremental cost effectiveness ratio (CER), measured from the employer and the societal perspectives. Input data were obtained from a variety of published sources. For 100,000 exposed workers, surveillance resulted in 683 fewer cases of disability over 10 years. Surveillance conferred benefits at an incremental cost of $24,000/QALY (employer perspective;	2++	Mathematical simulation model	Isocyanates	100,000

	$13.33/SFD) and was cost saving from the societal perspective. Results were sensitive to assumptions about sensitisation rate, removal rates, and time to diagnosis, but not to assumptions about therapy costs and disability rates.				
Zuskin 1997 [121]	A follow-up investigation was performed on 49 female workers studied 2 years earlier in a vegetable-pickling plant. Acute and chronic respiratory symptoms and ventilatory capacity measurements were recorded during the original and the follow-up studies.		Cohort	Vegetable-pickling plant	49
Chapter 4: Primary prevention of occupational asthma: exposure reduction, skin exposure, respiratory protection (for more details including elaboration of references see [122]					
Ancillary question 1: "Evidence for prevention of asthma due to natural rubber latex (NRL)"					
Allmers 2002 [123]	Decreased use of powdered gloves and increased use of powder-free gloves correlated with decline in suspected NRL OA and skin allergy cases, 1997-2001. CONCLUSION: Primary prevention of occupational NRL allergies is possible with properly implemented practical interventions.	From LaMontagne 2006	Case series, reported number of suspected NRL allergy cases from German health care system	NRL exposure from gloves	3 million insured health care workers in Germany
Heilman 1996 [124]	Latex aeroallergen levels (ng/m3) and extractable latex glove allergen contents in an operating room measured on 52 consecutive days, including 19 non-surgery days, with 12 exposure crossovers. On 33 surgery days, all personnel wore either high allergen gloves (n = 18 days) or low allergen gloves (n = 15 days). Internal comparison (cross-over). CONCLUSION: Substitution of low-allergen-NRL gloves for high-allergen NRL gloves can reduce latex aeroallergen levels by more than 10-fold in an OR environment.	From LaMontagne 2006	Prospective evaluation of an intervention	Operating room (OR) personnel exposed to NRL	Measurements on 52 days
Jones 2004 [125]	Studied dental students from 1st to last year in training. Students used only powder-free	From LaMontagne 2006	Prospective evaluation of	NRL exposure in dental students	63 dental students at baseline, 34 at final

	NRL gloves and were tested annually. Students were 65% atopic, but none developed latex sensitivity in 5 years of study. CONCLUSION: Exposure to powder-free NRL gloves was not associated with sensitization over 5 years in a highly atopic population.		intervention		year (loss to follow-up)
LaMontagne 2006 [126]	Substitution of powdered latex gloves with low protein powder-free NRL gloves or latex-free gloves greatly reduces NRL aeroallergens, NRL sensitisation, and NRL-asthma in healthcare workers.	Lit. search	Systematic review	Natural rubber latex (NRL) exposure	8 studies ranging from exposure studies and observational data from cohort studies
Lee 2001 [127]	Education to reduce NRL glove use in food handlers. Use was reduced from 10 stalls to 1. CONCLUSION: Educate food handlers to prevent NRL allergy in workers and customers.	From LaMontagne 2006	Intervention among food handlers in Australia	NRL glove use in food handlers	30 food stalls at market
Levy 1999 [128]	Last-year dental students in Paris, France, and London, England completed a questionnaire and skin prick testing with NRL extract. The odds ratio for latex sensitivity was 11.3 (95 % CI 2.4-53.0) for using protein-rich gloves. CONCLUSION: Use of powder-free protein poor NRL gloves may reduce latex sensitization.	From LaMontagne 2006	Cross-sectional: Some students had used protein-rich gloves and others had not	Use of protein-rich vs, protein poor NRL gloves in dental clinic	189 5th year (graduating) dental students working in clinics
Liss 2001 [129]	In 1996, Ontario government recommended change to powder-free, low-protein or non-NRL gloves in health care, and hospitals changed related policies about the same time. Researchers documented a decline in worker comp claims for NRL OA, from highs of 7-11/yr in 1991-94 to 1-2/yr in 1997-99. CONCLUSION: Use of low-protein or non-NRL gloves is associated with a decrease in number of NRL OA cases.	From LaMontagne 2006	Case series based on worker comp claims in Ontario province, Canada	Use of powdered NRL gloves and change to low-powder NRL and non-NRL gloves in health care facilities.	66 WC claims for NRL through 1999
Saary 2002 [130]	Dental school in Ontario province, Canada, changed from high protein/ powdered to low protein/ non-powdered NRL gloves. A	From LaMontagne 2006	Intervention for students and staff in dental	NRL gloves in dental school	131 in 1995 and 97 in 2000

	positive NRL skin prick test in students decreased from 10% in 1995 to 3% in 2000 (p=0.03). There was a decline in % with urticaria, immediate pruritis, and rhino-conjunctivitis, but not asthma or eczema. CONCLUSION: Suggestive preventive effect by change to low-protein/powder-free NRL gloves in dental school.		school, between cross-sectional surveys in 1995 and 2000 (two different study cohorts).		
Tarlo 2001 [116]	Study conducted in teaching hospital in Ontario, Canada. Intervention was education and medical surveillance, and change to powder-free NRL gloves. Decline in symptom onsets and clinic visits after change in non-sterile gloves in 1995 and sterile gloves in 1997, to final year of study in 1999. CONCLUSION: NRL allergy reduced.	From LaMontagne 2006	Intervention & retrospective record review to detect NRL allergy cases in occupational health and allergy clinics	NRL in gloves in hospital	8000 employees, 52 staff with positive skin test responses and clinical NRL allergy.
Ancillary question 2: "Evidence for prevention of asthma due to a variety of agents"					
Anhydrides					
Grammer 2002 [131]	Before introduction of respirators, annual incidence for asthma was 10%. During 7 years of follow-up after introduction of respirators, highest annual incidence was 2%. CONCLUSION: Respirators can reduce incidence of occupational immunologic respiratory disease, including OA, in workers exposed to hexahydrophthalic anhydride (HHPA)	2+	Prospective cohort study following intervention (introduction of respirators)	HHPA	66 new workers who made HHPA
Diisocyanates					
Tarlo 2002 [117]	In 1983, Ontario province in Canada mandated medical surveillance program for workers exposed to diisocyanates. This was followed by retrospective assessments to determine benefits. Frequency of diisocyanate asthma worker comp claims (both in number and % of all OA claims) rose to peak in 1988, and then declined significantly to 1993. CONCLUSION: Medical surveillance program contributed to	3 for surveillance and 2+ for case control study within case series.	Registry based ecologic study. Case series from worker comp claims for OA attributed to diisocyanates in province of Ontario, Canada.	Diisocyanate exposure (study had exposure above TLV as readout parameter.)	Number of claims varied by year, from high of 55-58 claims/yr in 1988-1990, to low of 19-20 claims by 1992-1993

	the positive change, but cannot rule out that reduced diisocyanate exposures and increased awareness of problem by workers and physicians may have also contributed to decline.				
Flour And Other Bakery Exposures					
Meijster 2009 [132]	Changes in exposure over time varied substantially between sectors and jobs. For bakeries: modest downward trend of -2%/yr for flour dust and -8%/yr for amylase. For flour mills: -12%/yr for flour dust and significant trend for amylase. For ingredient producers: results generally non-significant, but indicated a reduction in flour dust and increase in fungal alpha-amylase. Modest increase in use of control measures and proper work practices reported in most sectors, especially the use of local exhaust ventilation and decreased use of compressed air. CONCLUSION: The magnitude of the observed reductions in exposure levels indicates that the sector-wide intervention strategy implemented during the covenant period had a limited overall effect.	2+	Sector-wide intervention program, with education on good work practices, and non-randomised pre-post evaluation of exposure to wheat and fungal α-amylase	Bakery workers, flour millers, bakery ingredient workers	1770 personal exposure measurements generally including data on flour dust and fungal α-amylase levels, taken in 4 surveys (1993, 2001, 2005, 2007).
Smith 2004 [133]	Intervention was reducing bread improver levels by better exhaust ventilation, respiratory protection when handling bread improver, and education; respiratory health surveillance; and dust sampling. There was an overall reduction in the incidence of new cases of symptomatic sensitization, from 2085 per million employees per year in the first 5 years of the surveillance programme, to 405 per million employees per year in the subsequent 5 years. Symptomatic sensitization incidence was not related to total inhalable dust levels. CONCLUSION: The strategy of targeting	2-	Prospective intervention in UK food company. Based on surveillance data in combination with a triage approach which was not validated	Bakery workers, flour millers exposed to flour and enzymes, especially fungal amylase	>3000 workers per year under surveillance

	bread improver exposure is an effective approach for preventing new cases of symptomatic sensitization in bread bakeries.				
Detergent Enzymes					
Cathcart 1997 [134]	At five production facilities in the UK: studied dust and enzymes levels 1969-1993; lung function of workers 1972-1991, and cases of OA 1968-1992. Exposure groups were defined by job history. Enzyme levels declined over study period. Rates of fall in FEV1 and FVC showed no consistent trends in relationship to enzyme exposure. The annual number of cases of enzyme allergy and asthma declined.	2-	Registry based study, case series, ecological	Detergent enzyme exposure in production facilities	731 male workers
Schweigert 2000 [135]	Variety of controls introduced across detergent enzyme manufacturing industry. Decrease in number of OA cases in Latin American and North American detergent enzyme manufacturing sites 1969 – 1998, but no denominators indicated.	4	Review article with minimal data and documentation.	Detergent enzyme manufacturing industry	Unclear
Laboratory Animal Allergy and Asthma					
Botham 1987 [136]	Prospective studied incidence of allergy to laboratory animals (ALA) in 383 workers exposed to rodents and to rabbits. Intervention was introduction of a site order and code of practice for working with animals and an education programme. Concurrent with the intervention, incidence of allergy after 1 year of exposure to animals fell from 37% in 1980-81 to 20% in 1982, 10% in 1983, and 12% in 1984. Atopy increased risk of allergy in first year of exposure but not in 2^{nd} or 3^{rd} years of exposure.	2-	Intervention study with longitudinal, repeated measurements	Laboratory animal workers with exposure to rodents and rabbits	383 workers
Fisher 1998 [137]	Intervention program included education, engineering controls, administrative controls, use of personal protective equipment, and medical surveillance. They	2-	Comprehensive intervention program with longitudinal,	Laboratory animal workers	159 employees

	conducted a prospective survey of 5 years of data to determine effect program (1991-1995). At start of program, prevalence of laboratory animal allergy (LAA) was 12%-22% at first, and then 0% in last 2 years of the 5-year observation period. CONCLUSION: LAA is preventable through the implementation of a comprehensive effort to reduce exposure to allergens.		repeated measurements		
Ancillary question 3: "Selected References on occupational skin exposure to isocyanates"					
Bello 2008 [138]	Quantitative skin wipe sampling method developed. 92% of samples under PPE had detectable NCO levels, mostly pHDI. Highest total NCO concentrations associated with spraying and mixing.		Cross-sectional	HDI, auto body repair workers	185 samples from 81 auto body shop painters and techs during different tasks. 43 samples under PPE
Fent 2008 [139]	Log-transformed concentrations of HDI (r-0.79, $p<0.001$) in skin of workers correlated with log-transformed product of air concentration and painting time. Other polyisocyanates detected on skin for less than 25% of paint tasks.		Cross-sectional	HDI, auto body spray painters	13 auto body spray painters – air and skin concentrations
Fent 2009 [140]	Isocyanurate predominant isocyanate. Dermal HDI concentrations higher in those not wearing gloves/coveralls. NCO detected on skin during 23% of paint tasks. Linear mixed modeling identified breathing-zone concentration and paint time significant predictors skin concentration.		Cross-sectional	HDI, auto body spray painters	47 spray painters dermal and inhalational exposure assessment 15 painters no gloves
Flack 2009 [141]	- HDA detected in 76% plasma samples. - Correlation between plasma HDA and same day dermal exposures low but significant, correlation between HDA and 20-60 day dermal exposure higher (r=0.36)		Cohort	HDI, auto body shop painters	46 spray painters - blood, inhalation and dermal exposures measured. 288 tasks.
Liljelind 2010 [142]	Average personal air concentrations below Swedish exposure limit. Tape tripping used measure MDI skin exposure. Decreasing levels of MDI in consecutive tape strips per site indicate dermal penetration.		Cross-sectional	MDI, iron-foundry workers	19 workers in different areas of foundry – tape strip dermal sampling repeated on five exposed skin areas

					and air sampling
Liu 2009 [143]	Skin exposure algorithm using diaries, task based skin sampling, PPE. Median daily SEI (skin exposure index) estimated for each worker. Was associated with job category. Weakly correlated with daily airborne exposure.		Cross-sectional	Workers in auto body shops	232 workers in 33 shops. 893 exposure person-days skin exposure, work diary
Pronk 2006 [144]	- Inhalation HDI exposure associated with tasks involving aerosolisation. Dermal exposure assessed by extraction HDI from nitrile gloves; associated with paint-handling tasks, glove use. - HDA detected in 36% of repair shop workers, 10% of industrial workers. - HDA significantly elevated at end of workday. HDI oligomers main exposure.		Cross-sectional Pre-post shift sampling	HDI (mostly oligomers), auto body repair workers	A) 68 task-based paired inhalation and dermal samples from 6 auto repair shops. 239 urine samples from 45 workers B) 27 paired inhalation and dermal samples fm 5 industrial paint co. 52 urine samples from 10 painters.
Robert 2007 [145]	- MDA detectable in 73% of post-shift urine samples. These levels significantly higher than pre-shift levels. - Highest MDA levels associated with spraying or hot processes. Skin exposure associated with significant MDA levels in urine.		Cross-sectional	MDI, polyurethane workers	169 workers of 19 French factories and 120 controls
Todd 2008 [146]	- 8-21% of workers exposed to mixtures of chemicals (solvents, HDI) > OELs; 39-69% of surface samples positive for un-reacted isocyanates using qualitative CLI SWYPES^{TM}. - PPE, IH controls not adequate.		Cross-sectional	Workers at footwear and equipment factories	286 personal air samples, 64 surface, tool, or hand samples from 4 factories in Thailand
Ancillary question 4: "References which address the association between skin exposure and asthma"					
Bernstein 1993 [48, 147]	Based on questionnaire-derived diagnoses of 243 workers: 4% workers occupational asthma (OA), 36% occupational rhinitis, 11% irritant lower respiratory symptoms. 2 / 243 (0.4%) MDI-specific IgG – both worked in finishing area where they had direct MDI skin contact. Plant designed to minimize	3	Cross-sectional / case series isocyanate asthma	MDI, urethane mold plant	243 workers exposed to MDI – questionnaire and serum antibody tests. 147 workers on urethane mold lines. 3 cases isocyanate

	exposures MDI. 24-hr / day air monitoring area samples. All air levels < 0.005 ppm over 3 yrs. Selected workers further medical evaluation: 3 cases OA from MDI (1.2%) and 1 case MDI-induced cutaneous anaphylaxis (positive MDI-HSA skin test and MDI-IgE). These 4 workers worked in areas with potential MDI skin contact – maintenance and finish area. 1 case MDI asthma onset of symptoms after MDI spill. Conclusions: Low prevalence of sensitization (MDI-IgG) and OA. Recommend avoid MDI skin contact.				asthma
Dernehl 1966 [148]	Mentions personal experience isocyanate skin exposure increases risk asthma.	3	Personal experience	MDI	Workers with respirator protection and repeated skin contact
Donnelly 2004 [149]	Nurse with MDI asthma. Case confirmed by specific inhalation challenge with MDI cast material (39% decreased FEV1).	3	Case study	MDI, hospital – synthetic plaster casts	1 nurse working with MDI-containing plaster casts for 4 years
Lenaerts-Langanke 1992 [150]	Population 1) Half reported skin exposure. 6.5% (14/216 pressure grouters) MDI-related respiratory symptoms. 4/216 pressure grouters isocyanate hyper-responsiveness, 2 positive MDI-specific inhalation challenge. Air exposures very low (<1 ppb) Population 3 – 6/8 pressure grouters with heavy skin exposure MDI metabolites in urine. Skin irritation MDI rare – only 1 in all workers. MDI skin exposure common, “typical phenomenon”. MDI sensitization through skin contact possible. Important prevent skin exposure.	3	Cross-sectional	MDI, coal miners	3 populations: 1) 284 total: 216 pressure grouters – inject MDI polyurethane (PU) foam; 55 control miners 2) 245 exposed miners 3) 8 pressure grouters with heavy PU skin exposure
Nemery 1993 [151]	Surface worker who handled half-empty MDI drums at the mine without safety precautions developed probable isocyanate	3	Case study	MDI, coal miners	Surface worker from coal mine

	asthma. Risk of isocyanate exposure with polyurethane rock consolidation. Cite Lenaerts – skin most likely sensitization.				
Petsonk 2000 [152]	27% of workers in areas with high potential for liquid MDI exposure reported new-onset asthma-like symptoms, versus 0% in low-potential areas. Skin staining and MDI on clothes, working around and cleaning up MDI was associated with new asthma-like symptoms. Follow-up asthma symptoms were associated with variable airflow limitation and MDI-specific IgE, not allergy skin prick testing. Air monitoring data (6 personal breathing zone samples) no detectable MDI. A single glove wipe sample was taken and had 0.078 mg MDI. Conclusions: Skin may be site for potential immunologic sensitization and subsequent risk for development of respiratory symptoms.	2+	Cohort (1 year follow-up)	MDI, wood manufacturing plant	214 plant employees, 83% participated in follow-up survey. Questionnaires prior to use of MDI and every 6 months afterwards. Serial peak flows, spirometry, methacholine challenge, MDI-IgE, skin prick testing performed certain times, selected workers
Shahzad 2006 [153]	Asthma prevalence 10.8% (69/641). Multivariate analysis –asthma associated with educational status, ethnicity, smoking, glove use (never use OR=3.28; 95% CI: 1.72-6.26), perceived allergy, duration of work. Protective effect glove use may be due to protection skin from sensitizing chemicals.	2-	Cross-sectional	Leather tannery workers in Pakistan	641 workers in 95 tanneries, all workers enrolled working with tanning process. Questionnaire. No exposure information.
Ancillary question 5: "Evidence for effectiveness of respirators to prevent onset of occupational asthma"					
Grammer 2002 [154]	Before introduction of respirators, annual incidence for asthma was 10%. During 7 years after respirators introduced, highest annua20l incidence was 2%. Authors concluded respirators can reduce incidence of occupational immunologic respiratory disease, including OA, in workers exposed to hexahydrophthalic anhydride (HHPA)	2+	Prospective cohort; following intervention (introduce respirators)	Acid anhydride	66 new workers who made HHPA

Online supplementary TABLE sO4 Major causative agents for work-related asthma

(see also following references with lists of agents and corresponding reviews) [155-161]
http://www.uke.de/institute/arbeitsmedizin/downloads/universitaetsprofessur-arbeitsmedizin/R42_und_R37A-EU09.pdf;
http://www.uke.de/institute/arbeitsmedizin/downloads/universitaetsprofessur-arbeitsmedizin/Table_2_Irritants.pdf;
http://www.worldallergy.org/professional/allergic_diseases_center/occupational_allergens/;
www.asmanet.com; www.asthme.csst.qc.ca; http://www.occupationalasthma.com

Flour/grain dust
Isocyanates
Paints
Laboratory animals and insects
Enzymes
Wood dust
Bioaerosols containing moulds and bacteria
Latex
Seafood (crab, prawn, shellfish)
Persulfates, bleaches
Cutting oils and coolants
Anhydrides
Solder/colophony/welding fumes
Acrylates and acrylics
Cleaning products
Formaldehyde, glutaraldehyde
Platinum salts
Cobalt
Nickel sulphate, chromium
Spills of irritants such as chlorine, acetic acid, smoke from fires

Online supplementary text sO5

Clinical outcome of work-related asthma

In total, our literature search identified 88 papers which had evaluated the outcome of WRA [2, 4, 5, 8-19, 21, 37, 38, 43, 48, 53, 54, 75, 77, 85, 162-186] [36, 42, 187] [22-28, 33, 34, 39, 46, 50, 51, 55, 56, 110, 119, 188-205]. Sixty-one of the 88 papers focused on specific exposures in cohort studies or case series. Of those, isocyanates (24), anhydrides (7), latex (6), and red cedar (5) were the most frequently studied exposures. Seventy-one of 88 studies (81 %) were published in 2000 or earlier. In addition to symptoms and lung function, the variables used to evaluate the outcome of asthma have included both NSBHR [9-11, 13, 14, 38, 42, 43, 75, 85, 163, 164, 171, 175, 179-182, 187] [18, 19, 21-28, 46, 50, 54, 183, 185, 189-195, 197, 198, 200-203, 205], and specific immunogical responses (specific IgE [25, 42, 77, 164, 172-174, 177, 178, 199, 205], specific IgG [25, 77, 172, 173, 178], and specific bronchial responsiveness) [11, 18, 28, 53, 54, 179, 187, 188, 200, 202, 203]. Fewer studies were available concerning measurements of inflammatory activity, which included those that used induced sputum [13, 38, 43, 46], BAL [167, 190, 193] or fractional exhaled nitric oxide (FeNO) [38]. Bronchial biopsy studies were uncommon [50, 193, 197, 198]. In addition, other outcomes researchers investigated were employment [15, 16, 33, 37, 39, 42, 85, 110, 162, 166, 168, 175, 182, 185] and income [37, 85, 162, 166, 182, 185], assessment of asthma severity [8, 185] and QoL [180, 181, 187].

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