

**MANAGEMENT OF OCCUPATIONAL ASTHMA: CESSATION OR REDUCTION OF EXPOSURE? A SYSTEMATIC REVIEW OF AVAILABLE EVIDENCE**

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**ABSTRACT**

Background: Reduction of exposure to sensitizing agents causing occupational asthma (OA) has been proposed as an alternative to total avoidance in order to minimize the adverse socio-economic impact of the condition.

Objectives: The aim of this systematic review was to compare the effects of these two management options on asthma and socio-economic outcomes.

Methods: A bibliographic search was conducted to identify studies examining the outcome of workers with OA after reduction or cessation of exposure to the causal agent.

Results: The changes in asthma symptoms and nonspecific bronchial hyperresponsiveness after reduction or cessation of exposure were respectively described in nine and five studies, respectively. The meta-analysis of pooled data showed that a reduction of exposure was associated with a lower likelihood of improvement (OR [95% CI]: 0.16 [0.03-0.91]) and recovery (OR: 0.30 [0.11-0.84]) of asthma symptoms and a higher risk of worsening of the symptoms (OR: 10.23 [2.97-35.28]) and NSBHR (OR: 5.65 [1.11-28.82]) as compared with complete avoidance of exposure.

Conclusions: This systematic review indicates that reduction of exposure cannot be routinely recommended as an alternative to cessation of exposure in the management of OA. However, further investigations are required before drawing evidence-based conclusions on the cost-effectiveness of this approach.

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**Keywords:** Asthma, occupational disease

**List of abbreviations**

FEV<sub>1</sub>: Forced expiratory volume in one second

NSBHR: Non-specific bronchial hyperresponsiveness

OA: Occupational asthma

## INTRODUCTION

Over the past few years, work-related asthma has increasingly been recognized as a public health concern due to its high prevalence [1]; approximately 15% of asthma in adults is attributable to the workplace environment [2]. In addition, work-related asthma significantly contributes to the global burden of asthma through its long-term respiratory health and socio-economic consequences [3, 4]. For immunologically-mediated occupational asthma (OA) (i.e. '*sensitizer-induced OA*' or '*allergic OA*' or '*OA with a latency period*'), the general therapeutic recommendation is to remove the affected workers from exposure to the causal agent [5, 6], since continued exposure may result in the worsening of symptoms, airway obstruction, and non-specific bronchial hyperresponsiveness (NSBHR) [7]. However, avoidance of exposure is associated with a substantial adverse socio-economic impact, because maintaining the affected worker at the same job after elimination of the hazard from the workplace or relocating of the worker to an unexposed job is often not feasible.

Recent clinical practice guidelines have acknowledged that the reduction of exposure may lead to an improvement or resolution of asthma and thus, could be considered an alternative to complete avoidance in order to minimize the socio-economic impact of OA when elimination of exposure is not feasible or unexposed jobs are not available [5, 6]. However, the long-term effectiveness and safety of this management option remain largely uncertain [7].

The objective of this systematic review was to analyze the available data comparing the long-term health and socio-economic outcome of subjects with OA after reduction or cessation of exposure to the aetiological agent. This review aimed at providing information to physicians, patients, employers, and policy makers based on the best available medical evidence.

## **METHODS**

### **Bibliographic Search**

Publications examining the outcome of OA after reduction of exposure to the causative agent were identified through a PubMed search of articles published in any language up to December 2009. This systematic analysis was completed as part of a general review of the best available evidence on the management of work-related asthma conducted by a Task Force of the European Respiratory Society. The strategy used for the electronic search is available as online material (Online supplement 1). Abstracts of the retrieved papers were carefully analyzed in order to identify original studies pertaining to the outcome of workers with “lower”, “reduced”, or “intermittent” exposures. The reference lists of relevant articles and previous systematic reviews [7, 8] were screened in order to identify any additional publications.

### **Selection Criteria**

The review was restricted to studies that presented a direct comparison between the outcome of workers with immunologically-mediated OA who reduced their exposure and those who completely avoided exposure to the offending agent. The following exclusion criteria were applied: 1) studies of “irritant-induced asthma” and “work-exacerbated asthma”; 2) studies evaluating the clinical effects of a reduction of exposure (e.g. with personal protective equipment) during laboratory or workplace challenges; and 3) case reports, meeting abstracts, and review articles. When multiple studies assessed serially over time the same, or a portion of the same, cohort of workers with OA, the most recent report or the publication providing the most appropriate data was selected.

### **Data Collection and Analysis**

Data were extracted using a standard record sheet by one reviewer and checked for completeness and accuracy by a second reviewer. The collected information pertained to the baseline demographic and clinical characteristics of the workers (sex, age, smoking status,

atopy, severity of asthma); the agent(s) causing OA; the procedure used for diagnosing OA; the duration of exposure and asthma symptoms; the nature of the interventions (reduction vs. cessation of exposure); and the duration of the follow-up.

Considering the substantial heterogeneity of reported clinical and functional outcomes in follow-up studies of OA [7, 8], it was *a priori* decided to restrict the analysis to the outcome of asthma symptoms and NSBHR, which were categorized as “recovered”, “improved”, or “worsened” according to the criteria used in each study. Data pertaining to socio-economic outcomes (employment, loss of income, health-care costs, and quality of life) were also gathered when available. The methodological quality of the relevant studies was not formally assessed, but potential biases and confounding factors were recorded [9]. Because of the small number of available studies, no attempt was made to explicitly evaluate the effects of potential confounders, for example, demographic characteristics of the subjects at baseline, atopy, smoking habits, anti-asthma treatment, molecular-weight category of the agent, duration of exposure to the agent, and duration of follow-up.

The meta-analysis of the pre-determined outcomes (i.e. recovery, improvement, or worsening of asthma symptoms and NSBHR) was conducted using the MetaAnalyst Beta 3.13 software [10]. In this meta-analysis, 'recovery' was considered a subcategory of 'improvement' and was analysed either separately or combined with the 'improvement' group. The heterogeneity within the results of the studies was assessed using the Cochran Q test and was considered significant when the p value was  $<0.10$ . The results were summarized as the odds ratios (ORs) and 95% confidence intervals (95% CIs) for each outcome among workers who reduced exposure as compared with those who avoided exposure using either a fixed-effect or a random-effect model according to the presence of significant heterogeneity. The pooled prevalence estimates of each outcome after reduction or cessation of exposure were computed using a random-effect model. The draft evidence



report was reviewed by all members of the ERS Task Force on the Management of Work-related Asthma.

## RESULTS

### Characteristics of Included Studies

The bibliographic search identified 114 publications, from which we selected 32 original studies pertaining to the outcome of “reduced exposure”. Of these 32 publications, ten studies met the inclusion criteria and were included in the analysis (Table 1) [11-20]. ~~Of the 32 initially retrieved studies pertaining to the outcome of “reduced exposure”, 22~~ Twenty-two articles were excluded for the following reasons: 1) lack of a comparison group of workers who avoided exposure [21-27]; 2) comparison with asymptomatic workers who remained exposed to the offending agent [28]; 3) serial assessments of the same or a portion of the same cohort of workers with OA due to red cedar dust [13, 29-33], isocyanates [34], or persulphate salts [35]; 4) failure to provide appropriate data on the outcomes of patients who had “reduced exposure” [36-40], and 5) single case report [41].

Eight of the ten selected publications involved a longitudinal follow-up of patients recruited from specialized clinics [11-16, 18, 20], although the mode of selection of the participants and their participation rate were not clearly stated in four studies [12-15]. Two studies were retrospective surveys of patients whose functional parameters were not assessed before environmental interventions [17, 19]. The studies included 478 patients with OA (median sample size of the studies: 28; 25<sup>th</sup>-75<sup>th</sup> percentiles: 22-64); 186 patients (median per study: 18; 25<sup>th</sup>-75<sup>th</sup> percentiles: 8-26) had reduced exposure and 292 (median: 12; 25<sup>th</sup>-75<sup>th</sup> percentiles: 7-26) had avoided exposure to the causal agent. The most commonly identified causal agents (seven of ten publications) were low-molecular-weight agents, including isocyanates [12, 15, 16], colophony [11], red cedar dust [13], platinum salts [17], and persulphate salts [20], while only two studies involved a high-molecular-weight agent (i.e. natural rubber latex) [18, 19], and one study evaluated patients with OA caused by various agents, of which 90% were low-molecular-weight agents [14]. The diagnosis of OA was established by a positive specific inhalation test in seven studies [11, 13-16, 18, 20] or

the combination of a positive immunological test with functional assessments (i.e. specific inhalation challenge in the laboratory and/or monitoring of peak expiratory flow rates at work) [12, 17], or with a consistent clinical history [19] .

The interventions aimed at reducing exposure are summarized in Table 1; none of the studies provided quantitative assessments of exposure before or after the intervention. The baseline characteristics of the workers who reduced exposure were compared to those of the workers who ceased exposure in five of the eight prospective follow-up studies [13, 15, 16, 18]. These comparisons provided inconsistent findings across the studies; reduction of exposure being associated either with a lower baseline FEV<sub>1</sub> [11], or a younger age and a shorter duration of exposure before intervention [15], or an older age and a longer duration of exposure [16], or less frequent treatment with inhaled corticosteroids [18], or a higher proportion of atopics [13]. The median or mean follow-up periods ranged from 14 to 63 months. Five studies did not compare the duration of follow-up in workers who reduced and those who avoided exposure [12, 14, 16, 17, 19]. The duration of the follow-up did not differ among the two groups in four studies [11, 13, 15, 18], while it was longer for the patients with reduced exposure in one study [20]. Changes in asthma medications during the follow-up period were described in four of ten studies [15, 16, 18, 20], and only one study reported on the changes in smoking habits [16].

### **Effects of Interventions on Asthma Symptoms**

Nine publications described the outcome of asthma symptoms after reduction (179 patients) or cessation (283 patients) of exposure using the following categorization: complete resolution (nine studies, 462 patients), improvement (five studies, 164 patients), or worsening (five studies, 119 patients) (Table 2) [11-14, 16-20]. Most (six out of nine) of these studies relied on a qualitative assessment of the changes in asthma symptoms while only three studies used a quantified symptom score [16, 18]. Pisati et al. [16] analyzed the changes in asthma status using a score that combined symptoms, medications, and the changes in

FEV<sub>1</sub> and NSBHR (Table 2). The study by Vandenplas et al. [18] reported the median values of an asthma severity score that was derived from the frequency of asthma symptoms, the need for asthma medications, and hospital admissions, but also provided the proportion of patients who recovered from their asthma, as defined by the absence of symptoms and anti-asthma medication. Munoz et al. [20] graded asthma severity according to the criteria proposed by the Global Initiative for Asthma guidelines.

The meta-analysis of the pooled data (Table 3) showed that the reduction of exposure was associated with a lower likelihood of improvement (OR [95% CI]: 0.16 [0.03-0.91]) and recovery (OR [95% CI]: 0.30 [0.11-0.84]) from asthma symptoms and a higher risk of symptom worsening (OR [95% CI]: 10.23 [2.97-35.28]) as compared with avoidance of exposure (Figure 1).

### **Effects of Interventions on Non-specific Bronchial Hyperresponsiveness**

Five studies evaluated the changes in NSBHR after reduction (44 patients) or cessation (66 patients) of exposure (Table 4) [11, 12, 15, 18, 20]. The level of NSBHR was assessed using various methods; the five publications stated the threshold concentration or dose of a pharmacological agent (i.e. acetylcholine, histamine, or methacholine) to achieve a specified bronchial response that was considered as reflecting a level of NSBHR in the asthmatic range. Recovery from NSBHR was considered when these threshold concentrations or doses exceeded the cut-off values for asthma at the follow-up assessment (Table 4). The magnitude of the change in the concentration or dose of pharmacological agent at follow-up assessment that was considered as being significant was not clearly stated in two studies and was assigned a threshold value of one doubling concentration or dose [11, 12] .

The meta-analysis of changes in NSBHR (Table 3) revealed that reduction of exposure was associated with a significantly higher risk of NSBHR worsening (OR [95% CI]: 5.65 [1.11-28.82]) as compared with cessation of exposure (Figure 2).

### **Socio-economic Outcomes**

Five of the ten publications [11, 14, 15, 18, 19] provided some socio-economic information, but the employment status at the follow-up visit was clearly stated in only two studies of workers with OA caused by colophony [11] and natural rubber latex gloves [18]. These studies revealed that the proportion of currently employed workers was significantly higher among those who reduced exposure (8/8 in colophony-induced OA and 20/20 in latex-induced OA) as compared to those who avoided exposure (7/20 in colophony-induced OA,  $p=0.004$  and 9/16 in latex-induced OA,  $p=0.003$ ). The study by Vandenas et al. [18] reported that a major loss of income was more frequent in subjects with latex-induced OA who ceased exposure to latex (9/16) than in subjects who remained exposed to reduced levels of latex (3/20,  $p=0.023$ ). The median actual reduction in earnings was 20% from the initial value (25th-75th percentiles: 0-51%) after avoidance of exposure and 0% (25th-75th percentiles: 0-16%,  $p=0.038$ ) after the reduction of exposure. Asthma-related quality of life at the follow-up visit did not differ between the two groups.

## DISCUSSION

### Findings

This meta-analysis of ten studies including 478 subjects with OA showed that reducing exposure to the causal agent was associated with a lower likelihood of improvement and recovery of asthma symptoms and a higher risk of worsening of symptoms and NSBHR as compared with complete avoidance of exposure. These findings do not provide sufficient evidence for using exposure reduction as a management option in patients with OA and they further support the statements that reduction of exposure “*is not always effective*” [5] and that “*there is little evidence for using this approach*” [6]. The systematic review on the management of OA by Beach and co-workers [7] examined the outcome of symptoms [11, 12, 17, 18, 22, 23, 26, 27, 41], medications [11, 12, 18, 23, 35], FEV<sub>1</sub>, [11, 12, 18], and NSBHR [11, 12, 18] after the reduction of exposure in studies published up to 2004. The authors concluded that the majority of the studies on subjects who reduced exposure reported the following: some improvement in asthma symptoms; no clear pattern of changes in medication use; an improvement in FEV<sub>1</sub> over time in less than half of the studies; and there were insufficient data (improvement in one of three studies) to draw conclusions about the changes in NSBHR. In contrast to Beach and co-workers, we deliberately opted to restrict our review to publications that allowed for a direct comparison between workers who reduced and those who avoided exposure to the offending agent. Moreover, we analyzed the changes in symptoms and NSBHR after the interventions in a simple, categorical manner (i.e. recovery, improvement, and worsening) as proposed by Rachiotis and co-workers in their systematic review of the outcome of OA after avoidance of exposure [8]. Six [22, 23, 26, 27, 35, 41] of the ten studies [11, 12, 17, 18, 22, 23, 26, 27, 35, 41] on workers with reduced exposure in the review by Beach and co-workers [7] were excluded from our analysis because they did not match our pre-defined inclusion criteria. On the other hand, we analyzed six studies [13-16, 19, 20] that were not included in the review of Beach and co-

workers [7]. Noticeably, the cohorts of workers who avoided exposure that were selected in our review did not differ from those examined by Rachiotis and co-workers [8]. The rates of symptoms and NSBHR recovery after cessation of exposure that were found in our review (38%, 95% CI: 29-48% and 29%, 95% CI: 10-59%, respectively) were similar to those reported by Rachiotis and co-workers (32%, 95% CI 26-38% and 27%, 95% CI: 21-34%) [8].

Very few studies provided analyzable information on socio-economic outcomes. Two studies found that the reduction of exposure resulted in a lower rate of unemployment than the avoidance of exposure [11, 18]. Accordingly, it remains uncertain whether reducing exposure results in a lower socio-economic impact than complete avoidance of exposure.

### **Limitations**

A number of methodological weaknesses of this systematic review should be carefully considered before drawing definitive conclusions for clinical practice. First, available studies have a high – though unquantifiable – potential for selection bias since all publications were observational follow-up studies where the rationale for the intervention decision (i.e. reduction vs. avoidance of exposure) was largely unknown. Noticeably, the proportion of subjects who avoided exposure was markedly higher as compared to those who reduced exposure in most studies involving low-molecular-weight agents (i.e. 2.3 to 3.2-fold higher) [11-14, 16, 20]. By contrast, reduction of exposure was a more common intervention than avoidance (i.e. 1.2 to 5.0-fold more common) only for workers with OA due to latex [18, 19] and platinum [17]. This suggests that the outcome of reducing exposure has been mainly investigated in some specific work environments and that the observed effects may not be extrapolated to other settings. In addition, it is possible to speculate that subjects with more severe asthma had the tendency to avoid rather than reduce exposure to the causal agent. In the five studies comparing the baseline clinical data of the subjects, there was no clear indication that those who reduced exposure to the causal agent had a less severe asthma than those who avoided exposure [11, 13, 15, 16, 18], with the exception of the study by

Vandenplas et al., in which the subjects who ceased exposure to latex allergens were more frequently treated with inhaled corticosteroids than those who reduced exposure [18]. Beach and co-workers compared the baseline FEV<sub>1</sub> in cohorts of subjects with OA who continued or avoided exposure and concluded that lung function at diagnosis was not associated with exposure status during follow-up [7]. However, it should be acknowledged that prospective randomized controlled trials of the effectiveness of various management approaches will never be conducted due to ethical considerations.

Second, information regarding “baseline” workplace exposures, the interventions taken to reduce exposures, and the effectiveness of such interventions was very limited. None of the included studies relied on quantitative exposure assessments to document reduction of exposure, although quantifying the reduction of exposure may be difficult due to the day-to-day variability in the level of exposure in most workplaces. Nevertheless, the interventions aimed at reducing exposure to asthmagens, such as the use of personal protective equipment, engineering changes to the workplace, or the relocation of the worker to area or job with decreased exposure, were in most cases, not clearly described. Therefore, it was not possible to take into account the actual magnitude of the reduction in the level of exposure achieved in each cohort. In addition, none of the interventions were based on an *a priori* definition of what should be a biologically relevant reduction of exposure.

Third, significant between-study heterogeneity was observed for both studied outcomes, with the exception of symptom worsening and changes in the level of NSBHR. Included studies were very heterogeneous in their sample size, methods of assessment, and outcome reporting. Therefore, it was not possible to control for potential confounders, such as atopic status, history of asthma pre-existing to the causal exposure, the duration of symptoms before the intervention, and changes in smoking habits and asthma treatment during the follow-up period. There was also considerable within-study heterogeneity since available studies included workers with very different types of exposure to the same agent,



for instance workers exposed to various types of isocyanates in different industries [12, 16]. In addition, most of the studies did not use standardized, validated instruments for assessing the severity or control of asthma symptoms and their impact on quality of life.

Finally, the major limitation of this review relates to the low generalisability of its findings. Thus, it was not possible to separately analyze the outcome of the interventions according to the nature of the causal agents since most of available publications (i.e. eight out of ten cohorts) involved populations exposed to low-molecular-weight agents. Furthermore, studies pertaining to high-molecular-weight agents were restricted to natural rubber latex gloves. For instance, a large majority of the studies reporting on the improvement of asthma symptoms (Figure 1, middle panel) [11, 12, 14, 16, 19, 20] and the worsening of symptoms [14, 16, 19, 20] and NSBHR [11, 12, 15, 20] assessed populations with OA due to LMW agents, mainly isocyanates (Figure 1, lower panel and Figure 2, lower panel). ~~Visual inspection of Forest plots for symptom recovery (Figures 1, upper panel) suggests that the difference between the effects of reduction and avoidance of exposure on asthma symptoms was less in workers exposed to agents acting through an IgE-mediated mechanism (i.e. latex and platinum salts) [17-19].~~

## **Conclusions**

This systematic review of available evidence found that reduction of exposure to agents causing OA is associated with in a less beneficial effect on asthma outcome than complete avoidance. These findings indicate that the reduction of exposure cannot be routinely advocated as an alternative to the cessation of exposure. However, the limited quality of available studies prevents us from drawing definitive conclusion on the effectiveness and safety of reducing exposure to occupational asthmagens. Moreover, there is insufficient data to compare the socio-economic consequences of these two management approaches. There is a clear need for further investigation of the cost-effectiveness of the different management options of OA caused by various agents through prospective & large-

scale studies based on outcomes that have been validated for the evaluation of asthma and quantitative evaluation of interventions aimed at reducing exposure.

**Table 1. Description of Included Studies**

Reference	Country	Agent	Design	Intervention	No. of subjects	Duration of follow-up (months)
Burge PS, 1982[11]	UK	Colophony	Longitudinal follow-up. Clinic-based.	Alternative job in the same factory	28	Mean: 27-29; Range: 12-45
Rosenberg N, 1987[12]	France	Isocyanates (various types)	Longitudinal follow-up. Clinic-based.	Alternative job with intermittent exposure (n=4) or same job with improved conditions (n=3)	27	Mean: 17; Range: 1-66
Chan-Yeung M, 1987[13]	Canada	Red cedar	Longitudinal follow-up. Clinic-based.	Alternative area or job with intermittent exposure	178	Mean: 48
Moscato G, 1993[14]	Italy	Various (90% LMW agents)	Longitudinal follow-up. Clinic-based.	Alternative job with intermittent exposure	25	Mean: 14, SE: 2
Paggiaro PL, 1993[15]	Italy	Isocyanates (TDI)	Longitudinal follow-up. Clinic-based.	Alternative area with occasional exposure (less than once a week for less than 15 min)	16	Median: 48; Range: 18-73
Pisati G, 1993[16]	Italy	Isocyanates (TDI)	Longitudinal follow-up. Clinic-based.	Alternative area with intermittent exposure; 15/17 subjects used personal protective equipments (paper mask or cartridge respirator)	60	Mean: 60; SD: 7
Merget R, 1999[17]	Germany	Platinum salts	Retrospective cross-sectional cohort study. Clinic-based.	Alternative job in the production building but not directly involved in production or outside of the production building	74	Median: 54; 25 <sup>th</sup> -75 <sup>th</sup> percentiles: 23-84
Vandenplas O, 2002[18]	Belgium	Latex	Longitudinal follow-up. Clinic-based.	Exposure to less than 20 pairs of powdered latex gloves per week in the vicinity or only low-allergen sterile latex gloves used together with latex-free examination gloves.	36	Median: 56; Range: 12-92.
Bernstein DI, 2003[19]	USA	Latex	Retrospective study of subjects recruited by advertisement	Switch to non-latex gloves (n=19) but indirect exposure from co-workers using powdered latex gloves in 12 subjects; area transfer in 1 subject.	24	Mean: 47
Munoz X, 2008 [20]	Spain	Persulfate salts	Longitudinal follow-up. Clinic-based.	Same job but no direct contact with persulfate salts	10	Mean 63; SD: 19; Range: 39-101.

**Legend:** LMW = low molecular weight.

**Table 2. Reported Outcome of Asthma Symptoms**

Reference	Agent	Reduction of exposure			Cessation of exposure		
		Recovered	Improved*	Worse	Recovered	Improved*	Worse
Burge PS, 1982[11]	Colophony	1/8	6/8	NA	4/20	20/20	0/20
Rosenberg N, 1987[12]	Isocyanates	0/7	4/7	2/7	10/20	14/20	NA
Chan-Yeung M, 1987[13]	Red cedar	0/42	NA	NA	55/136	NA	NA
Moscato G, 1993[14]	Various	0/7	4/7	0/7	9/18	18/18	0/18
Pisati G, 1993[16]	Isocyanates	0/17†	0/17	13/17	12/43†	22/43	5/43
Merget R, 1999[17]	Platinum salts	25/55	NA	NA	10/19	NA	NA
Vandenplas O, 2002[18]	Latex	4/20	NA	NA	3/16	NA	NA
Bernstein DI, 2003[19]	Latex	20/20	20/20	0/20	4/4	4/4	0/4
Munoz X, 2008[20]	Persulfate salts	0/3	NA	0/3	2/7	NA	0/7
Pooled estimate:		50/179 17.6% (5.9-42.0%)	34/59 60.1% (23.7-87.9%)	15/54 20.6% (3.8-63.5%)	109/283 38.2% (29.1-48.1%)	78/105 81.4% (55.2-94.0%)	5/92 8.8% (4.2-17.3%)

Legend: NA = not available.

\*: subjects with improved asthma symptoms including those who recovered;

†: Changes in asthma status were defined by a combination of parameters: (1) recovery = no symptoms, no medication for the past 12 months, normal FEV<sub>1</sub> and absence of NSBHR; (2) improvement or deterioration = significant change in symptom score (>1 grade on a 0-4 scale) or medication score (>1 grade on a 0-4 scale) together with a significant change in FEV<sub>1</sub> (>10% from initial value) or NSBHR (change in the dose of methacholine causing a 15% fall in FEV<sub>1</sub> >1 doubling dose).

**Table 3. Meta-analysis of the Impact of Cessation and Reduction of Exposure on Asthma Symptoms and Non-specific Bronchial Hyperresponsiveness**

Outcome	Test for heterogeneity	Reduction vs. cessation of exposure to the causal agent		
		Fixed effect model OR (95% CI)	Random effect model OR (95% CI)	
<i>Asthma symptoms:</i>	Recovery	p=0.037	NC	0.30 (0.11-0.84)
	Improvement	p=0.001	NC	0.16 (0.03-0.91)
	Worsening	p=0.114	10.23 (2.97-35.28)	4.00 (0.42-37.80)
<i>Non-specific bronchial hyperresponsiveness:</i>	Recovery	p=0.304	0.60 (0.18-2.00)	0.59 (0.15-2.30)
	Improvement	p=0.050	NC	0.50 (0.11-2.19)
	Worsening	p=0.884	5.65 (1.11-28.82)	5.65 (1.11-28.82)

Legend: NC = not computed due to the presence of significant heterogeneity.

Table 4. Reported Outcome of Non-specific Bronchial Hyperresponsiveness

Reference	Agent	Assessment of NSBHR: cut-off values for asthma and significant improvement	Reduction of exposure			Cessation of exposure		
			NSBHR recovered ‡	NSBHR improved*	NSBHR worse	NSBHR recovered	NSBHR improved*	NSBHR worse
Burge PS, 1982[11]	Colophony	H PC <sub>20</sub> <32 mg/ml; >1 doubling concentration†	1/8	2/8	1/8	9/20	11/20	0/20
Rosenberg N, 1987[12]	Isocyanates	A PC <sub>15</sub> <0.1 mg/ml; >1 doubling concentration†	0/6	0/6	2/6	0/14	5/14	1/14
Paggiaro PL, 1993[15]	Isocyanates	M PD <sub>20</sub> <1 mg; >1 doubling dose	3/7	4/7	0/7	3/9	5/9	0/9
Vandenplas O, 2002[18]	Latex	H PC <sub>20</sub> <16 mg/ml; >3-fold increase in PC <sub>20</sub>	1/20	15/20	NA	0/16	8/16	NA
Munoz X, 2008 [20]	Persulfate salts	M PC <sub>20</sub> <8 mg/ml; >3.2-fold increase in PC <sub>20</sub>	0/3	0/3	1/3	5/7	6/7	0/7
Pooled estimate:			5/44 15.5% (5.7- 35.5%)	21/44 39.1% (14.7- 70.5%)	4/24 21.4% (8.5- 44.2%)	17/66 28.8% (10.1- 59.3%)	35/66 51.9% (39.3- 64.2%)	1/50 5.2% (1.5- 16.4%)

Legend: A = acetylcholine; CU = cumulative unit; H = histamine; M = methacholine; NA = not available; NSBHR = non-specific bronchial hyperresponsiveness; PC/PD<sub>15-20</sub> = concentration of the pharmacological agent inducing a 15 or 20% fall in forced expiratory volume in one second; PD<sub>50</sub> sG<sub>aw</sub> = concentration of the pharmacological agent inducing a 50% decrease in specific airway conductance.

\*: Subjects with improved non-specific bronchial hyperresponsiveness including those who recovered;

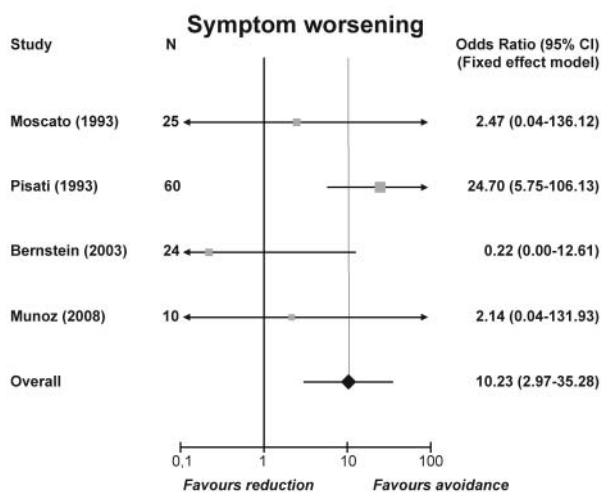
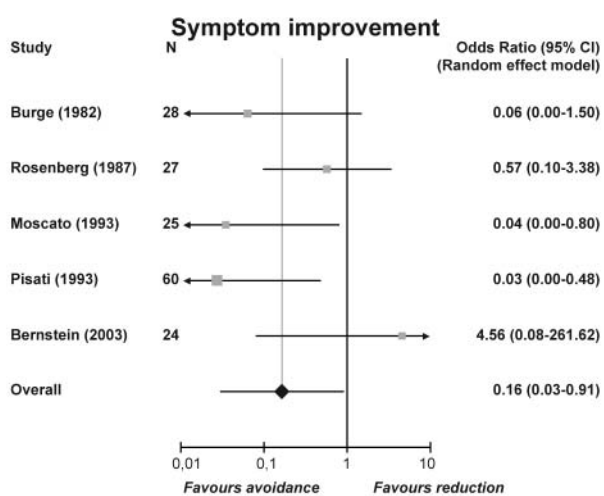
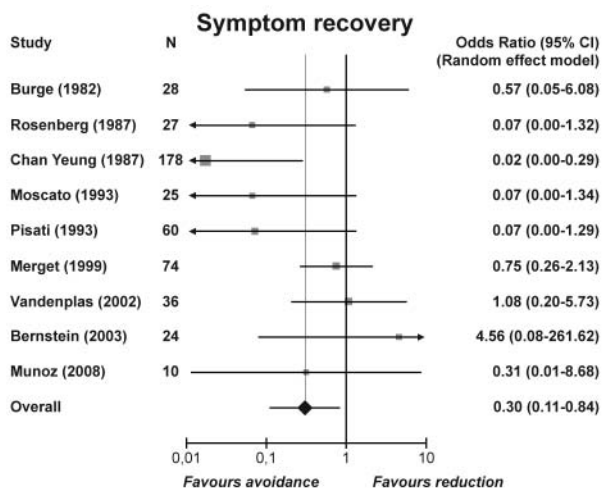
†: Threshold value for a significant change assigned by the authors.  
‡: Recovery from NSBHR was considered when the concentration or dose of the pharmacological agent inducing the specified functional change exceeded the cut-off value for asthma at the follow-up assessment.

## LEGEND TO FIGURES

### Figure 1

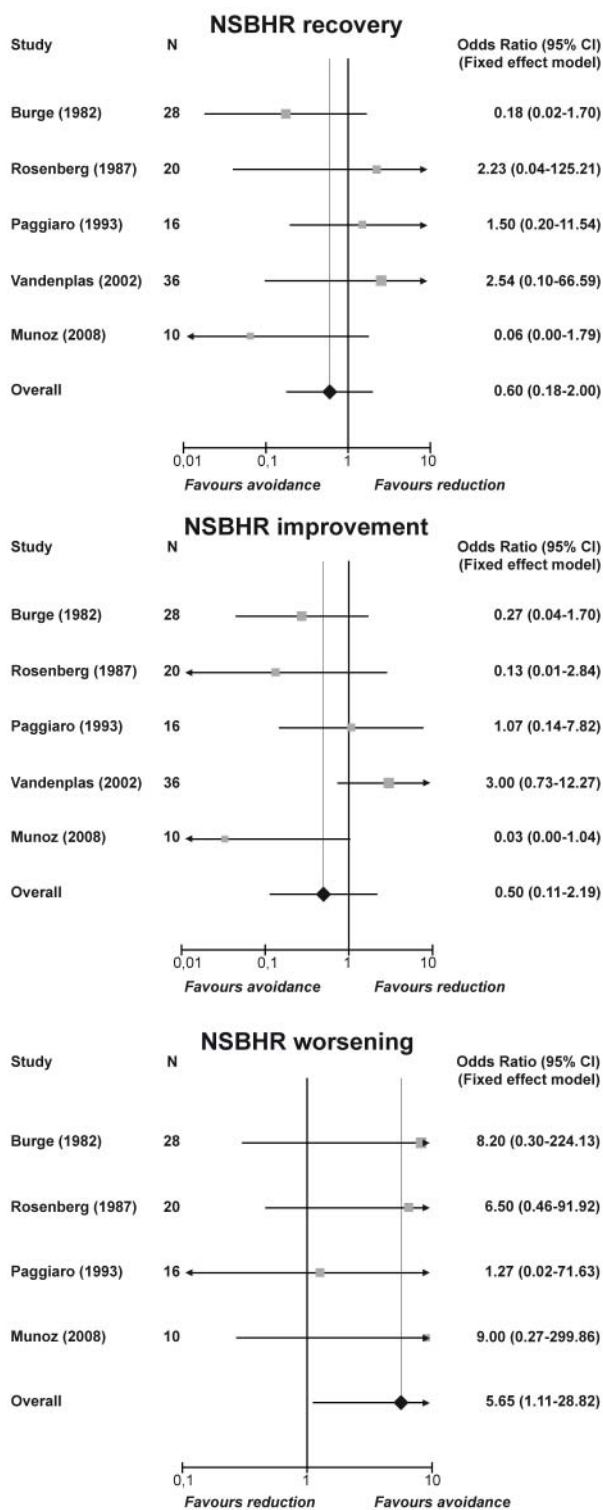
Forest plot of the comparison of the outcome of asthma symptoms: Recovery (upper panel), improvement (middle panel), and worsening (lower panel).





**Figure 2**

Forest plot of the comparison of the outcome of non-specific bronchial hyperresponsiveness: Recovery (upper panel), improvement (middle panel), and worsening (lower panel). NSBHR = non-specific bronchial hyperresponsiveness.





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## ONLINE REPOSITORY MATERIAL

### 1. Bibliographic search strategy

1. ("Asthma"[Mesh] OR "Hypersensitivity"[Mesh]) AND ("Occupational exposure"[Mesh] OR "Occupational Diseases"[Mesh] OR "occupational"[all]) AND (("reduction"[all] OR "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]).

2. ("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 "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]).

Note: The search strategy 2 was intended to incorporate different interventions that can be implemented for reducing exposure (i.e. “engineering control”, “relocation”, “prevention and control”, and “Threshold Limit Values”) and to broaden the identification of occupational asthma by introducing the terms "work related" and “work-aggravated”.