



Review

IgE-mediated sensitisation, rhinitis and asthma from occupational exposures Smoking as a model for airborne adjuvants?

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Received 26 April 2005; received in revised form 22 July 2005; accepted 28 July 2005

Abstract

Objective: Airborne pollutants with adjuvant effect, called airborne adjuvants, may promote IgE-sensitisation and development of allergic airway diseases. Smoking and occupational allergen exposures were reviewed to establish a general and verified framework for hazard identification and risk assessment of adjuvant effects of airborne pollutions.

Methods: The relative risks and the attributable risks of adjuvant effect of smoking were determined for co-exposures with green coffee and castor beans, ispaghula, senna, psyllium, flour and grain dust, latex, laboratory animals, seafood, enzymes, platinum salts, organic anhydrides, or reactive dyes.

Results: Adjuvant effects of smoking depended on the types of allergen, but not on whether sensitisation or allergy was promoted by atopy—the hereditarily increased ability to increase IgE formation.

Conclusion: Promotion of IgE sensitisation in humans and in animals may serve for hazard identification of adjuvant effects. Risk assessment has been based mainly on epidemiological studies, which are sensitive to confounding factors. This highlights the need to develop appropriate animal models for risk assessment.

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Keywords: Allergy; Adjuvant effect; Smoking; Hazard identification; Risk assessment

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1. Introduction

Occupational asthma has been suggested as a model for allergic asthma in the general population (Gautrin et al., 2003; Malo and Chan-Yeung, 2001), as the pathogenesis and pathological alterations are similar (Mapp et al., 1999). Also, offending exposures may be more easily identified in occupational settings (Mapp et al., 1999) where exposures constitute “natural experiments” (Venables et al., 1989). Exposures to high-molecular weight immunogens or to some low-molecular weight haptens may cause development of specific IgE antibodies that may result in IgE-mediated rhinitis, conjunctivitis and asthma (Malo and Chan-Yeung, 2001; Siracusa et al., 2000; Venables and Chan-Yeung, 1997). Development of allergic airway disease occurs in an allergen exposure-dependent manner (Gautrin et al., 2003; Nielsen et al., 2002; Malo and Chan-Yeung, 2001). Modifying factors may either enhance the development of specific IgE and allergic airway diseases, as with adjuvants including diesel exhaust (Pandya et al., 2002), or they may counteract the development, which may be the case with exposures to livestock farming or to oro-faecal pathogens (Braun-Fahrlander, 2003). The role of adjuvants as promoters of immune responses is well established within the vaccine area (Cox and Coulter, 1997; Marciani, 2003; Petrovsky and Aguilar, 2004), but the role of environmental adjuvants in the development of allergen specific IgE antibodies and IgE-

mediated allergic airway diseases is less clear. Nevertheless, environmental tobacco smoke has been correlated with development of asthma in children (Halken et al., 1995; Lewis et al., 2005) and shown to interact with several gene regions that have been linked to development of asthma and asthma-related phenotypes (Colilla et al., 2003). In this review, we use occupational allergen exposures and smoking, which is an occupational adjuvant on IgE-mediated allergies (Niven and Pickering, 1999), to highlight the natural history of smoking as a model adjuvant on the IgE-mediated processes—the IgE-mediated processes are those relevant for the airway allergies in the general population (Nielsen et al., 2002). Thus, the overall purpose of this study was to develop and verify a framework for evaluation of airborne pollutions as adjuvants on IgE-mediated allergies that may be useful for risk assessment of other environmental exposures. Although several models have been published to outline the processes of allergic airway diseases (e.g. Johnson et al., 2002; Karol, 1994; Malo and Chan-Yeung, 2001; Ring et al., 2001), these models do not selectively address hazard identification and risk assessment of environmental exposures, nor were they validated for this purpose.

The development of the proposed model by means of the most extensively reported occupational adjuvant, smoking, showed that the experiences from humans have several limitations. Animal studies are well established within elucidation of immunological mechanisms and

for hazard identification of adjuvant effects. However, more emphasis should be given to developing and implementing such models in risk assessment of environmental adjuvants.

2. Retrieval of literature and evaluation of studies

First, systematic literature searches were performed in PubMed, covering the period 1966–2004. General search profiles, “smoking AND asthma AND occupational” and “occupational asthma AND adjuvant”, were used to identify exposure types, which were associated with adjuvant effects and to establish specific search profiles. The specific search profiles were “allergen AND asthma AND smoking”, “allergen AND rhinitis AND smoking”, “allergen AND asthma AND review” and “allergen AND rhinitis AND review”. “Allergen” was coffee bean(s), castor bean, ispaghula, psyllium, senna, grain dust, latex, seafood, fish, enzyme, platinum, acid anhydrides and reactive dye(s) or it was replaced by informative words, such as “bakers”, “bakery”, or “laboratory AND animal”. The first two of the specific profiles were used to obtain relevant studies and the last two profiles were used to obtain a few recent reviews, which were scrutinized to obtain missing references. Also, the reviews were used to establish the context of exposures and the allergen properties. Studies written in English or German were considered.

If four or more informative cohort studies were retrieved the adjuvant effect of smoking was assessed from these studies. If less than four cohort-studies were available, case–control and cross-sectional studies were included. Cross-sectional studies were taken cautiously as they may underestimate associations because symptomatic workers may have left the job, the so-called “healthy worker effect” selection.

Studies with less than nine respondents were excluded as they probably have low power and might suffer from publication bias. Indication of the proportion of smokers in a study allowed the number of active smoking individuals to be obtained. If the number of smokers was compared to the remaining part of the population, this part was assumed to consist of never (non)-smokers and ex-smokers, if not otherwise indicated.

Health impacts were evaluated from the relative risk (RR) and the (workplace) attributable risk (AR) (WHO, 2000), for details cf. Appendix A. No AR was calculated if the RR was not increased significantly. Preferred studies were those where RR was directly available or could be calculated from the data in the study. Otherwise, if a significant effect of smoking was mentioned, but no

specific value was reported on a well-defined endpoint (e.g. “a statistically significant increased prevalence of skin prick test (SPT) positive individuals”), this was indicated by $RR > 1$. However, studies reporting a general statement as “there was no effect of smoking” were not considered. Also, if a newer longitudinal study was available from a group, their earlier cross-sectional studies were not considered if the population of these studies were judged to be included, at least partly, in the newer study.

The influence of atopy on allergen-induced specific IgE antibody production or diseases was mentioned if included in the references, which were used for evaluation of adjuvant effects or included in quoted reviews. Atopy was accepted to be present if reported in a study, irrespective of the definition. Thus, atopy may be defined as being sensitised to common aeroallergens, determined either by skin prick tests or by determination of specific IgE antibodies, having increased total IgE, or having a family or personal history of allergy (Charpin et al., 1988).

3. Immunologic endpoints

IgE-mediated airway diseases can arise from exposures to high molecular weight proteins or peptides, which are engulfed by the antigen-presenting (dendritic) cells (DCs). The DCs process the allergens and present allergen fragments to T cells, where the type 2 helper (Th2) T cells produce a number of interleukins (ILs). Among these, IL-4 and IL-13 promote synthesis of allergen-specific IgE antibodies by B cells (Corry and Kheradmand, 1999).

Reactive low molecular weight compounds may act as haptens, i.e. they may react with proteins on or in the body under formation of new allergens. The local DCs may degrade the new allergens and present the fragments for Th2 cells in the local lymph node; processes that have been reviewed recently (Lutz and Palczynski, 2003). After this, the following steps in the production of specific IgE antibodies proceed in the same manner as for the high molecular weight allergens.

Formation of allergen-specific IgE antibodies is a key event in the process of developing allergic asthma and rhinitis (Johnson et al., 2002; Platts-Mills, 2001). Also, this is supported by the fact that treatment of asthmatics with an anti-IgE antibody ameliorated exacerbations of asthma (Lanier et al., 2003). If sensitised, it increases the risk of developing airway allergy (Johnson et al., 2002; Platts-Mills, 2001). Thus, a recent comprehensive risk assessment of allergy from occupational exposures to flour dust was based exclusively on specific IgE

formation (DECOS, 2002). In consequence, specific IgE formation was selected as one endpoint in this study.

The IgE antibodies are carried by the blood, and upon contact with mast cells they occupy their high affinity IgE receptors (FcεRI). At re-exposure to the allergen, IgE on the receptors are cross-linked and the mast cells secrete biologically active compounds, including histamine, leukotrienes, prostaglandins and cytokines. This may cause an allergic reaction and result in an attack of urticaria, rhinitis, conjunctivitis and/or asthma (Corry and Kheradmand, 1999). However, as the genetic background, infection, types of allergen exposure, early life events, nutrition, obesity, and effects on the innate immune system, which includes activation of toll-like receptors, also play a role in the development of the IgE-mediated airway diseases (Buss et al., 2004), they may influence the possibility of detecting an adjuvant effect by means of studies in humans. Nevertheless, as the study of promotion of allergic diseases is the ultimate aim, airway diseases were used as other endpoints, where data existed.

Atopy was included in the study as gene-environmental interactions are important for the development of sensitisation and IgE-mediated allergies (e.g. Chipps, 2004; Johnson et al., 2002).

4. Adjuvants

The vaccine area allows insight into adjuvant mechanisms and of these, three may be relevant in relation to exposures to environmental adjuvants. First, solid or oily particles may form “particle–antigen complexes”, which may facilitate antigen delivery or presentation to the immune system, either by a slow release process or by facilitating uptake of the complexes into DCs (Cox and Coulter, 1997; Marciani, 2003; Petrovsky and Aguilar, 2004). A second mechanism of immune activation is due to stimulation of pattern recognition receptors (PRRs), including toll-like receptors, by microbial products (Marciani, 2003; Petrovsky and Aguilar, 2004). Finally, adjuvants may promote the immunological processes from the uptake of antigens into DCs and into the production of antibodies (Cox and Coulter, 1997; Marciani, 2003; Petrovsky and Aguilar, 2004).

The two combustion products, diesel exhaust particles (DEP) (Pandya et al., 2002; Riedl and Diaz-Sanchez, 2005) and tobacco smoke (Niven and Pickering, 1999), are pollutants that have commonly been associated with adjuvant effect. The adjuvant mechanisms for DEP are by far the best researched, but the two products have many mechanisms in common.

Briefly, DEP showed inflammatory effects, caused formation of IgE-mediated allergy-promoting cytokines (e.g. IL-4, IL-5 and granulocyte-macrophage colony-stimulating factor), and promotion of IgE production by B cells. The adjuvant effects have been ascribed to:

- transport of allergens into the airways due to association with DEP;
- formation of reactive oxygen species that may cause airway inflammation, and the promotion of processes in the cascade from the antigen presentation;
- the production of IgE (Pandya et al., 2002; Riedl and Diaz-Sanchez, 2005).

However, the allergen exposures in relation to traffic pollution are ill defined, which makes the adjuvant effect of DEP less suitable for development of a general framework for evaluation of adjuvant effects.

Tobacco smoke is a complex mixture of gases and vapours that contains approximately 6000 compounds (Johnson et al., 1990). Thus, it is tempting to speculate that the particulate phase may possess adjuvant effect, as is the case with particles in vaccines and from traffic pollution. Tobacco smoke is an airway irritant, it causes airway inflammation, it increases the airway epithelial permeability, and it is suppressive on many immunological endpoints. Exceptions are an increase in total leukocyte counts in peripheral blood, an increase in serum IgE, and an increase in macrophages in bronchopulmonary lavage fluid (Johnson et al., 1990). Airway inflammation may possess adjuvant effect (Granum and Løvik, 2002) and the increased permeability may cause increased access of the immune system to aeroallergens. Both of these may promote sensitisation. In contrast, lung macrophages are suppressive on immune responses (Holt and McMenamin, 1989) and thus, it might be inferred that the increased macrophage content might counteract airway allergies.

Tobacco smoke may affect several steps in the cascade from antigen presentation to formation of IgE. Thus, the heat sensitive capsaicin receptor (vanilloid receptor 1) has been identified on DCs. Stimulation by capsaicin caused up-regulation of antigen-presenting and co-stimulatory molecules, and promoted migration of DCs to the local lymph node (Basu and Srivastava, 2005). As capsaicin receptors may be activated by irritant gases and vapours (Nielsen, 1991), they may influence the sensitisation cascade. Nicotine is an important component of the particulate phase (Geng et al., 1995). It may change differentiation of DC precursors, causing changes in antigen-uptake and presentation, and in expression of chemotactic receptors and co-stimulatory

molecules, including up-regulation of CD86. The IL-12 production decreased in nicotine stimulated DCs (Guinet et al., 2004). The up-regulation of CD86 and the decrease in IL-12 might favour a Th2 stimulatory mode. Nicotine inhibited T cell proliferation (Geng et al., 1995), decreased the intracellular calcium response (Geng et al., 1995, 1996), and decreased a second messenger response (Geng et al., 1996) to T-cell receptor ligation. Also, ligation to antigen receptors showed a decreased calcium response in B cells (Geng et al., 1995). Smoke triggered mast cells to secrete histamine and rat basophilic leukaemia cells to secrete interleukins, including IL-4, which may be involved in proallergenic effects (Smyth et al., 2000).

As adjuvant and immunosuppressive effects of tobacco smoke can be due to a plethora of effects, this limits mechanistic interpretations. On the other hand, adjuvant effects of smoking offer a unique possibility to study exposure effects of an environmental adjuvant in humans. Furthermore, using occupational exposures allows determination of adjuvant effects in relation to different aeroallergens. We therefore used smoking and occupational exposures in order to establish a general framework for hazard identification and risk assessment of environmental adjuvant effects.

5. Adjuvant effects of smoking at exposures to high molecular weight allergens

In the general population, high molecular weight allergens are important in relation to development of allergic airway diseases, where the important aeroallergens are from house dust mites, cockroaches, pets, pollens, and moulds (Nielsen et al., 2002).

5.1. Green coffee beans and contamination with castor beans

Previously, green coffee beans (GCB) have sometimes been transported in sacks, which had also been used to transport castor beans (CB) (de Zotti et al., 1988; Osterman et al., 1982). Thus, in addition to the moderately potent GCB allergens, dust from GCB may have contained the potent allergens from CB (de Zotti et al., 1988; Osterman et al., 1982). However, during recent years new sacks have been used, reducing the exposure to CB allergens (Larese et al., 1998; Romano et al., 1995). Both types of allergens can cause specific IgE sensitisation in an exposure-dependent manner and development of IgE-mediated rhinitis, conjunctivitis and asthma (de Zotti et al., 1988; Osterman et al., 1982). Castor bean and GCB allergens show slight or no cross-reactivity

(Romano et al., 1995). Sensitisation of coffee industry workers (Larese et al., 1998; Osterman et al., 1982; Romano et al., 1995) and dock workers (de Zotti et al., 1988) was more prevalent among atopic individuals.

Studies on adjuvant effect of smoking and exposures to GCB and/or CB allergens are summarized in Table 1. In several of the studies, the relative risk was not statistically increased, but the median relative risk in smokers was fairly stable at around 2 for effects on sensitisation. The relative risk of clinical symptoms was about 1.6 in smokers in one study, but this value was not statistically significant. Overall, taking into account the limitations of cross-sectional studies, these studies support that smoking can possess adjuvant effect in relation to GCB and CB exposures with the ARs ranging from 0 to 64%.

5.2. *Ispaghula*, *senna* and *psyllium*

Ispaghula is the dried seeds of *Plantago ovata* and ispaghula husk is the epidermis of the seed. Psyllium consists of the seeds of *Plantago psyllium*. Both types of seeds are constituents of, for example, various laxative mixtures (Wallis, 1962). However, the medical literature does not always distinguish between the seeds. Also, senna leaves are used as a component of laxatives (Wallis, 1962). All three plant-products may cause specific IgE-mediated sensitisation and development of allergic rhinitis, conjunctivitis and asthma (McConnochie et al., 1990; Malo et al., 1990; Marks et al., 1991; Helin and Mäkinen-Kiljunen, 1996; Khalili et al., 2003). For psyllium, oral intake has caused anaphylaxis (Khalili et al., 2003).

Studies on adjuvant effects of smoking and exposures to ispaghula, senna and psyllium are summarized in Table 1. In three of the four studies, the relative risk was above one, however only one of these values was significant. Thus, no clear adjuvant effect of smoking was apparent with co-exposures to these allergens. The ARs ranged from 0 to 71%.

5.3. *Bakery* and *flour mill* dust

Bakers are exposed to several allergens, for example, flour and soybean proteins, enzymes for improving baking properties, storage mites from contaminated flours, and egg proteins, which may induce IgE antibodies and allergic rhinitis, conjunctivitis and asthma. Baker's asthma is among the most frequent forms of occupational asthma. Development of IgE antibodies and symptoms increase with increasing exposure levels, and atopy is an important risk factor as reviewed (Houba et al., 1998).

Table 1

Adjuvant effect of smoking in workers exposed to dust from green coffee beans, castor beans, ispaghula, senna and psyllium

Occupational exposure ^a	Allergen ^b	n/N ^c	Endpoint for study of adjuvant effect of smoking ^d	RR ^e	AR ^e	Reference
Coffee manufacturing	GCB	11/112	SPT to GCB	1.38 (NS)	–	Larese et al. (1998)
Coffee manufacturing	GCB + roasted coffee workers	47/211	SPT to GCB and/or CB	2.39	36	Romano et al. (1995)
Coffee manufacturing	GCB	13/52	Oculorhinitis and/or asthma	1.60 (NS)	–	Romano et al. (1995)
Coffee manufacturing	GCB	22/150	SPT to GCB; Sm + ex-Sm vs. non-Sm	>1	–	Thomas et al. (1991)
Dock workers	GCB + CB	20/218	SPT to GCB or CB	1.99 (NS)	–	de Zotti et al. (1988)
Coffee manufacturing	GCB	24/129	SPT to GCB	4.21	64	Zetterström et al. (1981)
Coffee manufacturing	CB	22/129	SPT to CB	2.87	50	Zetterström et al. (1981)
Pharmaceutical industry	Ispaghula and/or senna	21/118	SPT to ispaghula and/ or senna	1.30 (NS)	–	Marks et al. (1991)
Pharmaceutical industry	Ispaghula	9/92	IgE to ispaghula	0.74 (NS)	–	McConnochie et al. (1990)
Pharmaceutical industry	Ispaghula	9/60	IgE to ispaghula	4.97	71	Zetterström et al. (1981)
Chronic care hospital	Psyllium	18/124	IgE to psyllium; Ex-smokers excluded	1.43 (NS)	–	Malo et al. (1990)

^a All studies were of the cross-sectional design.^b Green coffee beans (GCB) and castor beans (CB).^c Indicated are total number of subjects (N) in the “population” and the number of cases (n) related to the endpoint from which the relative risk (RR) and attributable risk (AR) have been estimated.^d Skin prick test positive individuals used for the study of adjuvant effect of smoking are indicated by SPT and specific IgE formation by IgE. Smokers (Sm) were compared with the combined group of ex-smokers (ex-Sm) and non/never-smokers (non-Sm) if not otherwise indicated. Abbreviations of allergens are given in footnote b.^e Abbreviations as in footnote c.

However, about 30% of bakers with hyper-responsive and obstructive airways showed impaired lung function without specific IgE to occupational allergens; their reactions may be due to irritants, for example, emitted from hot ovens (Baur et al., 1998). Materials used in a bakery are suggested to be much more similar to those of normal life than to substances in industry (Baur et al., 1998).

Three cohort studies and one case–control study, where cases and controls were obtained from a cohort study, were retrieved from the literature search (Table 2). Additionally, one cohort study was identified with a low number of new sensitisations and thus not relevant for determination of adjuvant effects. Several cross-sectional studies were identified and evaluated, but they have not been reported. These studies may be less informative than the four key studies (Table 2). The case–control study (Cullinan et al., 2001) indicated that development of airway and eye symptoms and positive skin prick test responses to baking allergens were positively associated with exposure levels and that work-related symptoms were positively associated with positive skin prick tests. However, most of the incidence of eye, respiratory and skin symptoms could not be explained

from IgE-associated sensitisation to the two allergens studied.

Overall, the key studies showed no clear adjuvant effect of smoking, although all three-cohort studies had a non-significant increase in relative risk.

5.4. Grain dust

The composition of grain dust includes grain, grain and plant fragments, pollen, mites, insects, bacteria, fungi and inorganic components. It may induce asthma or asthma-like reactions both by an IgE and a non-IgE-mediated mechanism (Baur et al., 2003).

The effect of smoking was available from two Korean studies (Park et al., 1998a,b), which apparently were from the same animal feed industry. Grain-dust-specific IgE levels were positively associated with exposure levels to the dust. Adjuvant effects of smoking (Table 2) showed the same trend, which we calculated to be non-significant, as was observed in bakery and flour mill workers (Table 2).

5.5. Latex

Exposures to natural rubber latex may cause IgE-mediated asthma, rhinitis, urticaria and anaphylaxis due

Table 2
Adjuvant effect of smoking in bakery and flour-mill workers, grain-dust-exposed workers and hospital personnel

Occupational exposure	Allergen	Study ^a	Atopy promoted ^b	n/N ^c	Endpoint ^d for study of adjuvant effect of smoking	RR ^e	Reference
Bakers	Flour, α -amylase	Cohort 1 year	+SPT and/or IgE ^f	32/350	SPT and/or IgE: Sm vs. non-Sm + ex-Sm	1.64 NS	Walusiak et al. (2002)
Trainee bakers	Wheat, α -amylase	Cohort 0.6–2.5 years	0 S Atopy from SPT	10/125	SPT: Sm vs. non-Sm + ex-Sm	1.7 ^g NS	de Zotti and Bovenzi (2000)
Bakers	Bakery allergens	Cohort N.G. years	N.G.	M: 22/1029	A: Ever vs. non-Sm	1.6 ^h NS	Brisman and Järholm (1995)
Bakery and flour-mill workers	Wheat, α -amylase	Case 0.1–8 years	+SPT	21/42	SPT to wheat ⁱ	0.91 NS	Cullinan et al. (2001)
Animal feed industry	Grain dust	Cross	0 IgE	24/48 8-14/42-43	SPT to α -amylase ⁱ IgE: Ever vs. non-Sm	0.60 NS 1.59–3.03 NS	Park et al. (1998a,b)
Hospital personnel	Latex	Cross	+SPT	160/1326	SPT: Ever vs. non-Sm	0.88 NS	Liss et al. (1997)
Hospital personnel	Latex	Cross	+SPT	13/273	STP: Ever vs. non-Sm	0.99 NS	Vandenplas et al. (1995)

^a Cross-sectional (Cross), case–control (Case) and cohort study (Cohort) design are indicated together with the average time of follow-up in years (years). Not given is indicated by N.G.

^b If atopy influences reactions to the allergen in the second column, the endpoints, skin prick test (SPT) or specific IgE formation (IgE), or work-related respiratory symptoms (S), have been indicated as well as the direction, (+), (0) or not significant (NS).

^c For cohort and cross-sectional studies, the total number of subjects (N) in the “population” and the number of cases (n) are indicated. These values are related to the endpoint from which the relative risk (RR) has been obtained. In case–control studies cases/controls are indicated. Males are indicated by “M”.

^d Abbreviations as in footnote b. Asthma is indicated by A, smoking by Sm, non/never-smoking by non-Sm, ex-smoking by ex-Sm, and Sm + ex-Sm by ever Sm.

^e Relative risk.

^f Significant in the univariate analysis, but not confirmed by logistic regression.

^g Odds ratio from the reference.

^h Relative risk reported in the reference.

ⁱ Smokers vs. non-smokers, where smokers were workers who had smoked at least one cigarette daily for a year while employed at the site with allergen exposure.

to the content of numerous low molecular weight allergenic proteins (Cullinan et al., 2003; Weissman and Lewis, 2002). Atopy is a risk factor sensitisation to latex allergens (Charous et al., 2002; Cullinan et al., 2003; Weissman and Lewis, 2002). Exposures may be to multiple routes, e.g. skin contact, inhalation of aerosols, contact with catheters and gloves during surgery (Cullinan et al., 2003; Weissman and Lewis, 2002). Sensitisation occurs in an exposure-dependent manner in children with spina bifida (Charous et al., 2002; Weissman and Lewis, 2002). Latex allergy is mainly associated with powdered gloves (Charous et al., 2002) and skin contact may be an important exposure route (Weissman and Lewis, 2002). For development of latex-induced asthma, however, chronic airway exposures to latex allergens are required (Charous et al., 2002).

Two cross-sectional studies (Liss et al., 1997; Vandenplas et al., 1995) allowed evaluation of the adjuvant

effects of smoking (Table 2). Both studies showed that atopy promoted sensitisation to latex allergens. None of these studies showed that smoking promoted sensitisation and the numerical values of the RRs were close to one. Hives, wheeze and eye symptoms were more prevalent among sensitised individuals (Liss et al., 1997).

The lack of adjuvant effect may have several reasons. Smoking may simply have no adjuvant effect on sensitisation to latex allergens. However, other possibilities also exist. If a considerable part of the sensitisations occurred from latex allergens that penetrate the skin, the inhaled adjuvant and the allergens will not be presented at the same local part of the immune system. Similarly for inhalation, smoking and exposures to the allergens may not occur at the same time in hospital care workers (for explanations, cf. Section 7). Overall, an explanation of the lack of adjuvant effect may not be that simple.

5.6. Laboratory animals

IgE-mediated allergy—comprising skin reactions, rhinitis, conjunctivitis, asthma and in rare cases anaphylaxis—is common among individuals occupationally exposed to laboratory animals. Rhinitis and conjunctivitis are the most common type of reactions. Nevertheless, laboratory-animal-induced asthma is a common type of occupational asthma in general (Bush, 2001).

Studies on laboratory animal allergy and adjuvant effect of smoking are shown in Table 3. Exposure levels (Cullinan et al., 1994, 1999; Heederik et al., 1999) and atopy (Cullinan et al., 1994, 1999; Heederik et al., 1999) promoted development of specific sensitisation to laboratory animals and development of laboratory animal allergy symptoms (Kruize et al., 1997). Atopy promoted sensitisation especially at low allergen levels (Heederik et al., 1999). Also, atopy was associated with development of occupational asthma (Gautrin et al., 2001). Being sensitised to laboratory animals was a strong predictor of development of asthma (Gautrin et al., 2001).

The two cohort studies (Gautrin et al., 2001; Kruize et al., 1997) and the longitudinal study analysed as a case-control study (Cullinan et al., 1999) showed no significant adjuvant effect of smoking on sensitisation to laboratory animals (Table 3) in agreement with the recalculated values from the cross-sectional studies. Also, the study by Heederik et al. (1999), which was a cross-sectional study comprising several previous studies to increase statistical power, was in agreement with the cohort studies. Nor did the other cross-sectional studies show an adjuvant effect of smoking on the sensitisation phase. The eye and respiratory symptoms may be difficult to interpret, as exposures are complex and contain not only allergens, but also microbial components, which may include endotoxins and other irritants that may induce allergy-like symptoms.

5.7. Seafood

Occupational processing of seafood, including crabs, prawns, mussels and fish, may cause IgE sensitisation and IgE-mediated rhinitis, conjunctivitis, asthma and urticaria. Development of symptoms seems to follow dose-response relationships, atopy may be a risk factor and rhinoconjunctivitis and skin reactions often preceded asthma symptoms (Jeebhay et al., 2001).

Studies addressing the effect of smoking and exposures to seafood are shown in Table 3. In these studies, atopy promoted the development of specific IgE antibodies at prawn (McSharry et al., 1994) and snow crab processing (Cartier et al., 1984). In salmon processing

(Douglas et al., 1995), the prevalence of asthma was borderline increased by atopy ($p=0.06$). Similarly in snow crab processing (Cartier et al., 1984), asthma was increased, but not statistically significantly ($p=0.08$). In snow crab processing workers, being SPT positive to the crab allergen was significantly associated ($RR=5.93$, $p<0.001$) with occupational asthma. Nevertheless, several asthmatics were not SPT positive (Cartier et al., 1984). Also, a few workers developed fever and leukocytosis in relation to specific inhalation tests (Cartier et al., 1984). This suggested that different mechanisms could be involved in the reactions. However, in a follow-up investigation in a subpopulation of the snow crab exposed workers with more specific and more active extracts for skin prick testing and IgE determination, it was concluded that asthma triggered by exposure to the crab was mediated through an IgE mechanism (Cartier et al., 1986). Overall, the studies showed a statistically significant adjuvant effect of smoking either on the development of IgE antibodies or on the development of asthma (Table 3). The ARs were from >0 to 44%.

5.8. Enzymes

Production of proteolytic enzymes and their use in the detergent industry resulted in development of IgE-associated allergy. Reduction of enzyme levels reduced the appearance of new cases, i.e. the reactions were exposure-dependent. Industrial experiences showed that sensitisation was the first step in the process, and it was followed by upper respiratory tract reactions, which may later progress to asthma (Schweigert et al., 2000).

Several retrieved studies reported either promotion of sensitisation and allergic diseases or lack of promotion by smoking and atopy. However, only two studies, a minor study (Kizkin et al., 2002) and a comprehensive study (Johnsen et al., 1997), allowed estimation of RR and AR (Table 3). The comprehensive study clearly showed adjuvant effect of smoking, both on the specific IgE formation and allergic symptoms. Additionally, atopy was not an important risk factor (odds ratio = 1) in the comprehensive study and not a statistically significant risk factor in the minor study. The ARs ranged from 0 to 57%.

6. Adjuvant effect of smoking at exposures to low molecular weight haptens

Low molecular reactive compounds are mainly an industrial problem. However, they may appear, for example, from thermal degradation of indoor air dust

Table 3
Adjuvant effect of smoking in workers exposed to laboratory animals, seafood and enzyme containing detergents

Occupational exposure	Study ^a	n/N ^b	Endpoint ^c for study of adjuvant effect of smoking	RR ^d	AR ^d	Reference
Apprentices in animal-health technology	Cohort ~1–4 years	78/373	SPT (rat, mouse, rabbit)	0.85 NS		Gautrin et al. (2001)
		28/373	A	0.58 NS		
Newly employed animal workers	Case from a Cohort 0.1 to <8 years	46/92	SPT (rat)	1.18 NS	–	Cullinan et al. (1999)
		36/68	Chest symptoms	2.32	24	
Research institute	Cohort Average: 9.7 years	19/99	Incidence rate ratio of allergic skin, eye and respiratory symptoms	~1 NS	–	Kruize et al. (1997)
Laboratory animals facilities from Sweden, the Netherlands and the United Kingdom	Cross <4 years	63/649	IgE (rat); Sm vs. non-Sm; In: non-atopics	~1.35 ^e NS	–	Heederik et al. (1999)
			atopics individuals	0.9 ^e NS	–	
Animal breeders, technicians, scientists and zoo-keepers	Cross ≥1 year	9/60	A and/or R (guinea pig, rat, mouse, rabbit, hamster)	>6.17	>75	Krakowiak et al. (1997)
Laboratory animal workers	Cross	83/456	SPT (rat)	0.80 NS	–	Hollander et al. (1996)
		40/375	SPT (mouse)	0.62 NS	–	
Animal research institutions	Cross	21/238	SPT (rat)	1.80 NS	–	Cullinan et al. (1994)
Research facilities	Cross	51/296	SPT (rat, mouse, guinea pigs, rabbit)	1.40 NS	–	Venables et al. (1988b)
			Chest symptoms to laboratory animals	2.63	27	
Pharmaceutical company	Cross	15/138	Chest symptoms to laboratory animals	1.89 NS	–	Venables et al. (1988a)
Salmon processing	Cross	24/291	A (salmon)	>1 ^e	>0	Douglas et al. (1995)
Prawn processing	Cross	15/26	IgE (prawn) in symptomatic workers	2.36	42	McSharry et al. (1994)
Snow crab processing	Cross	43/263	A (crab)	2.20	44	Cartier et al. (1984)
Manufacturing of detergents with enzymes	Cohort 10 years	15/65	SPT (enzymes)	0.71 (NS)	–	Kizkin et al. (2002)
Manufacturing of enzymes	Cohort 0 to >3 years	76–355/995	IgE (enzymes)	1.26–3.33 ^f	13–57	Johnsen et al. (1997)
		94/1064	A/R/U (enzymes)	2.20	41	

^a Cross-sectional (cross), case–referent (case) or cohort study (cohort) design is indicated together with time of follow-up (years).

^b For cohort and cross-sectional studies are indicated total number of subjects (*N*) in the “population” and the number of cases (*n*) related to the endpoint from which the relative risk (RR) and the attributable risk (AR) have been calculated. In the case–referent study *n* is the number of cases and *N* is the number of controls.

^c Abbreviations for specific endpoints used for determination of adjuvant effect are: skin prick test (SPT), specific IgE (IgE), rhinitis (R), asthma (A) and urticaria (U). “Symptomatic workers” either had chest, upper airway, eye, or skin symptoms. Smokers (Sm) were compared to, non(never)-smokers (non-Sm) plus ex-smokers (ex-Sm) if not otherwise indicated.

^d Abbreviations as in footnote b. Not significant is indicated by NS.

^e Reported in the study.

^f Values depended on the selected cut points for a positive IgE level in the radioallergosorbent test.

(Pedersen et al., 2002) and from reaction of ozone with terpens in indoor air (Weschler, 2004).

6.1. Platinum salts

Halogenated platinum salts are intermediates in the process of refining platinum, reclaim of precious metals and production of catalysts (Merget et al., 2003). Platinum salts have little or no irritation potential. Exposures to platinum salts may cause formation of specific IgE that may easily be followed by development of allergic rhinitis and asthma, resulting in a high turnover of workers in platinum industries and thus bias of cross-sectional studies (Merget et al., 2003). Four cohort studies were available from the literature search (Table 4). Additionally, one cross-sectional study with information about adjuvant effect of smoking was also retrieved and included with the main purpose of adding information on the importance of atopy.

Where information was available (Table 4), studies showed a positive association between exposure and sensitisation. Atopy was not a statistically significant risk factor for development of sensitisation. An association was found between sensitisation and development of allergic eye, respiratory, or skin reactions (Niezborala and Garnier, 1996; Calverley et al., 1995; Venables et al., 1989; Baker et al., 1990). All studies showed a conspicuous adjuvant effect of smoking both evaluated from the RRs and the ARs (Table 4). The ARs ranged from 44 to 76%. Allergy-like symptoms from eyes, respiratory tract, or skin may occur without sensitisation (Calverley et al., 1995) or before sensitisation (Niezborala and Garnier, 1996; Venables et al., 1989), which may be due to the studied immunogen, effects of other immunogen exposures or due to irritant exposures.

6.2. Organic acid anhydrides

Organic acid anhydrides (AA) are used in production of alkyd, epoxy and polyester resins. AA can induce both irritant effects and different types of immunologic reactions. Thus, AA may induce IgE-mediated reactions, including asthma, which is assumed to be mainly due to inhalation, but sensitisation from skin contact is another possibility. IgG and/or cell mediated immune reactions may cause flu-like symptoms ("late respiratory systemic syndrome"), resembling symptoms from hypersensitivity pneumonitis. Another possible antibody-mediated reaction is pulmonary disease-anaemia, characterized by dyspnoea, pulmonary infiltration and haemorrhage, haemolysis and anaemia. The latter two types of reac-

tion are generally assumed to occur at high exposure levels (Zhang et al., 2002).

Allergy-like symptoms may be due to non-IgE-mediated reactions. In a cross-sectional study (Baur et al., 1995), 56 of 92 workers exposed to AAs had eye and/or respiratory symptoms. Rhinitis, cough, conjunctivitis and dyspnoea were present among 48, 26, 24 and 20%, respectively, whereas specific IgE was present in only 16% of the workers. Similar symptoms were found in other cross-sectional studies with exposures to phthalic anhydride (Nielsen et al., 1988; Wernfors et al., 1986) where non-IgE-mediated reactions played an important role. Thus, as the study of adjuvant effect may be confounded by symptoms from non-IgE-mediated processes, the evaluation of the adjuvant effect was limited to effects on the prevalence of IgE-mediated sensitisation (Table 5).

Two cohort studies were retrieved together with several cross-sectional studies (Table 5). Apparently, IgE sensitisation was exposure-dependent (Table 5), but atopy played only a limited role (Table 5). In one of the cohort studies, the adjuvant effect of smoking was rather small and not significant (Welinder et al., 2001), which was in agreement with the results from several cross-sectional studies conducted by the same group. As the populations in these studies were deemed to be, at least partly, included in the cohort study, they were not included in the present evaluation. However, the results from the cross-sectional studies support the consistency of the findings of the group. Overall, the two cohort studies suggest that the adjuvant effect of smoking may be highly variable (AR = 0–64%), which is in agreement with the results from the cross-sectional studies (Table 5). At least in one of the cross-sectional studies (Baur et al., 1995), "healthy worker effect" was suggested and thus the estimated RRs from the cross-sectional studies may be lower than the true RRs.

6.3. Reactive dyes

Reactive dyes are used as colouring agents in the textile industry. They may induce specific IgE antibodies and cause development of i.a. asthma (Park et al., 1991). We retrieved one study, which showed that smoking was an adjuvant and that atopy was not an important risk factor (Table 5). Smoking accounted for a high fraction of the sensitised subjects (AR ~ 80%). In this study, specific IgE antibodies accounted for a part of the asthma cases (AR = 54%), suggesting that other immunological or non-immunological mechanisms also may play a role (Park et al., 1991).

Table 4
Platinum salt exposures and adjuvant effect of smoking

Occupational exposure to platinum salts	Study ^a	Exposure promoted ^b	Atopy promoted ^c	n/N ^d	Endpoint ^e for determination of adjuvant effect of smoking	RR ^f	AR ^f	Reference
Catalyst production	Cohort 5 years	+SPT	0 SPT	13/115	SPT in the high exposed group. Sm vs. ex-Sm + non-Sm	3.9 ^g	57	Merget et al. (2000)
Refinery workers	Cohort ≤14 years	N.G.	No atopics	18/66	SPT. Sm vs. non-Sm	5.53 ^g	69	Niezborala and Garnier (1996)
				23/66	S (R/A/U/E). Sm vs. non-Sm	4.70 ^g	64	
Refinery workers	Cohort 2 years	+SPT	No atopics	22/78	SPT. Sm + ex-Sm vs. non-Sm	3.66	60	Calverley et al. (1995)
				32/78	SPT and/or S (R/C/A/U/E) Sm + ex-Sm vs. non-Sm	2.44	44	
Refinery workers	Cohort <8 years	N.G.	+SPT NS ^h	22/84	SPT. Sm vs. non-Sm	4.66 ^g	70	Venables et al. (1989)
				49/91	S (A/B) Sm vs. non-Sm	2.69 ^g	51	
Reclaim of precious metals	Cross	+SPT	SPT NS	23/135	SPT. Sm vs. ex-Sm + non-Sm	7.62	76	Baker et al. (1990)

^a Cross-sectional (cross) and cohort study (cohort) design is indicated. If reported, years (years) of exposure are indicated.

^b Platinum salt induced increase in an exposure-effect is indicated by “+” and not given by N.G. Exposure-effect shown by skin prick test is indicated by “SPT”.

^c If atopy influences development of allergy, a positive association has been indicated by (+), no association by (0) and not significant by (NS). If IgE antibodies were studied by skin prick test, it is indicated by SPT. If atopic individuals were excluded from the work force, it is indicated by “no atopics”.

^d The total number of subjects in the “population” is indicated by “N” and the number of cases by n. These values are related to the endpoint from which the relative risk (RR) and attributable risk (AR) were calculated.

^e Abbreviations are skin prick test (SPT), allergic symptoms (S) or diseases, i.e. allergic rhinitis (R), conjunctivitis (C), asthma (A), bronchitis (B), urticaria (U) or eczema (E). Smoking is indicated by Sm, ex-smoking by ex-Sm, and non(never)-smoking by non-Sm.

^f Abbreviations as in footnote d.

^g Adjusted RR, reported in the study. The RR and the fraction of smokers were used to calculate the AR value by means of Eq. (1) in Appendix A.

^h The relative risk and the 95% confidence limits, 2.29 (0.88–5.99), were given in the report.

7. Adjuvant effect in animal studies

7.1. Animal models and adjuvant effects

Due to the similarity of the immune systems in animals and humans, animal studies have offered major contributions to the understanding of the mechanisms of airway allergies in humans (Herz et al., 1996; van Houwelingen et al., 2001; Karol, 1994; Leong and Huston, 2001), which also highlights the value of predictive animal models.

Animal studies have addressed several questions about adjuvant effect, which epidemiological studies were not able to answer. Examples include:

What is the relationship between the administration of adjuvant and allergen, and an adjuvant effect? For particles, the maximum adjuvant effect was observed with co-administration, although administration of particles up to several days before administration of the allergen showed weak adjuvant effect if exposures were at the same site (Granum et al., 2001). For the airway irritant, NO₂, the maximum adjuvant effect was observed at inhalation of NO₂ about one day before the allergen exposure, where the airway inflammation was maximum (Siegel et al., 1997). Overall, the maximum adjuvant effect was apparent where adjuvant and allergen exposure occurred within a short time period, but that may depend on the adjuvant mechanism.

Table 5
Adjuvant effect of smoking in workers exposed to organic acid anhydrides and reactive dyes

Occupational exposure	Hapten ^a	Study ^b	Exposure promoted ^c	Atopy promoted ^c	n/N ^d	Endpoint ^e for determination of adjuvant effect of smoking	RR ^f	AR ^f	Reference
Use of epoxy resins	HHPA, MHHPA, MTHPA	Cohort 0.1–9 years	+IgE	+IgE	21/163	IgE (AAs)	1.70 (NS)	–	Welinder et al. (2001)
Resin and flooring manufacturing	PA, MA, TMA	Cohort 0.1 to <32 years	+SPT to TMA	SPT (NS)	12/374	SPT (AAs)	4.30	64	Barker et al. (1998)
Anhydride production	PA, MA, TMA, PMDA	Cross 0.6–41 years	–	IgE (NS)	15/90	IgE (AAs)	1.09 (NS)	–	Baur et al. (1995)
Use of epoxy resins	TCPA (colophony)	Cross	+IgE	–	15/45	IgE (TCPA)	0.31 ^g	–	Liss et al. (1993)
Use of epoxy resins	TCPA	Cross	+IgE	IgE (NS)	21/276	IgE (TCPA)	5.66	71	Taylor et al. (1987)
Use of epoxy resins	TCPA	Cross	–	IgE (NS)	24/300	IgE (TCPA)	4.80	66	Venables et al. (1985)
Dye-process workers	Reactive dyes	Cross	–	IgE ^h (NS)	48/261	IgE (black GR). Sm vs. non-Sm	12.9	88	Park et al. (1991)
				IgE ^h (NS)	40/261	IgE (orange 3R). Sm vs. non-Sm	6.94	79	

^a Organic acid anhydrides (AAs) are indicated as hexahydrophthalic anhydride (HHPA), methylhexahydrophthalic anhydride (MHHPA), methyltetrahydrophthalic anhydride (MTHPA), phthalic anhydride (PA), maleic anhydride (MA), trimellitic anhydride (TMA), pyromellitic dianhydride (PMDA; 1,2,4,5-benzene-tetracarboxylic dianhydride), and tetrachlorophthalic anhydride (TCPA).

^b Cross-sectional (cross) or cohort study (cohort) design is indicated. If reported, years (years) of exposure are indicated.

^c Organic acid anhydride induced increase in exposure-related response is indicated by “+” whereas not significant is indicated by NS. If exposure-effects were obtained from skin prick test, “SPT”, or from specific “IgE” formation, this is indicated. If atopy influences development of allergy, the endpoint and the direction have been indicated in a similar manner.

^d Indicated are total number of subjects (*N*) in the “population” and the number of cases (*n*) related to the endpoint from which the relative risk (RR) and attributable risk (AR) have been calculated.

^e Abbreviations as in footnote a and c. The endpoint was used for determination of RR and AR. The group of smokers, “Sm”, were compared with the combined group of non(never)-smokers, “non-Sm”, and ex-smokers if not otherwise stated.

^f Abbreviations as in footnote d.

^g Significantly decreased.

^h The IgE antibody corresponds to these in column 7.

What is the relationship between proximity of the place of adjuvant and allergen administration? A direct interaction is probably necessary if the adjuvant mechanisms are either due to a slow-release effect or to an enhanced uptake (targeting) in DCs as is the case, for example, with liposomes (Shek and Sabiston, 1981). Intraperitoneal (i.p.) administration of particles and intratracheal (i.t.) instillation of allergen showed far less adjuvant effect than if both were administered by i.t. instillation (Fujimaki et al., 1986). Thus, an optimal adjuvant effect may be seen, where the adjuvant and the allergen exposure occur at the same anatomical place. However, the effect may depend on the adjuvant mechanism.

Is there a dose-dependent effect of adjuvants? This seems to be the case, at least for particles (Fujimaki et al., 1986).

What is the importance of the exposure route for hazard identification? Co-administration of the combustion product, DEP, and an allergen showed adjuvant effect on the allergen-specific IgE formation from injection into the footpad, i.p., intranasal (i.n.), and i.t. administration, as well as by inhalation (cf. Granum et al., 2001; Larsen et al., 2004). Also, polystyrene particles showed adjuvant effect by i.p., i.n. and i.t. administration (Granum et al., 2001), which was also the case by aluminium hydroxide that was administered by subcutaneous and i.p. administration, and by inhalation (cf. Larsen et al., 2004). Overall, the route of exposure seems less important, which facilitates hazard identification of adjuvant effects. Nevertheless, as the airways are the port of entry of aeroallergen and air pollution (Steenenberget al., 2003), the airway route should be used for risk assessment.

7.2. Adjuvant effect of tobacco smoke

Only a few animal studies have dealt with the effect of smoking on sensitisation to airborne allergens. In one study, mice were exposed to a model allergen (ovalbumin, OVA), to side-stream smoke (environmental tobacco smoke, ETS) or to a combination. ETS showed a clear adjuvant effect on development of OVA specific IgE and IgG1 antibodies, both in a high and a low IgE-responder strain. Additionally, combined exposure to ETS and OVA increased the eosinophil content in bronchoalveolar lavage fluid (Rumold et al., 2001). Nevertheless in another study in three strains of mice, no adjuvant effect was apparent from ETS and OVA exposures on the IgG1 production (Bowles et al., 2005). In rats, combined exposures of cigarette smoke and OVA showed adjuvant effect on OVA

specific IgE and IgG production (Zetterström et al., 1985).

From the route and endpoints studied, formation of specific IgE and eosinophilic airway inflammation, were the same as the sentinel endpoints in humans. Tobacco smoke showed adjuvant effect in two of three animal studies, which is roughly similar to results in the epidemiological studies (Tables 1–5). Such variations may be explained, at least in part, by differences in exposure regimes (Clausen et al., 2003). Overall, it suggests that animal studies may reflect effects in humans and may be useful for hazard identification. However, for risk assessment, it will require that a quantitative relationship between effects in humans and animals is established. Also, taking the epidemiological and the animal studies together, this suggests that risk assessment models have to be further developed.

8. Model for adjuvant effect based on experiences from smoking

In general, a first step in the development of allergic airway inflammation and disease is assumed to be allergen-specific production of specific IgE antibodies (Malo and Chan-Yeung, 2001; Brochner and Busse, 2004), which is supported from industrial experience from exposures to enzymes in the detergent industry. In this case, sensitisation was followed by upper-respiratory-tract reactions, which may later progress to asthma (Schweigert et al., 2000). A general pattern seems to be that allergic rhinitis often precedes or accompanies the development of asthma (Boulay and Boulet, 2003), included in Fig. 1, track A. However, in several cases eye and/or airway symptoms appeared in more subjects than those being sensitised. This was observed with platinum salts, acid anhydride and reactive dyes exposures. The reactions may have been caused by other immunological or non-immunological mechanisms (Fig. 1, track B).

The studies (Tables 1–5) showed that sensitisation was promoted by increasing exposure levels to green coffee and castor beans, flour dust, latex, laboratory animal dust, seafood, enzymes, platinum, and organic acid anhydrides. Exposure-dependent development of symptoms was apparent from exposures to green coffee and castor beans, laboratory animals, seafood, and enzymes. Overall, the allergen exposure levels were important parameters in relation to development of allergic processes.

The hereditary background may influence all steps from sensitisation to development of allergic diseases and several genes have been linked to atopy, serum IgE

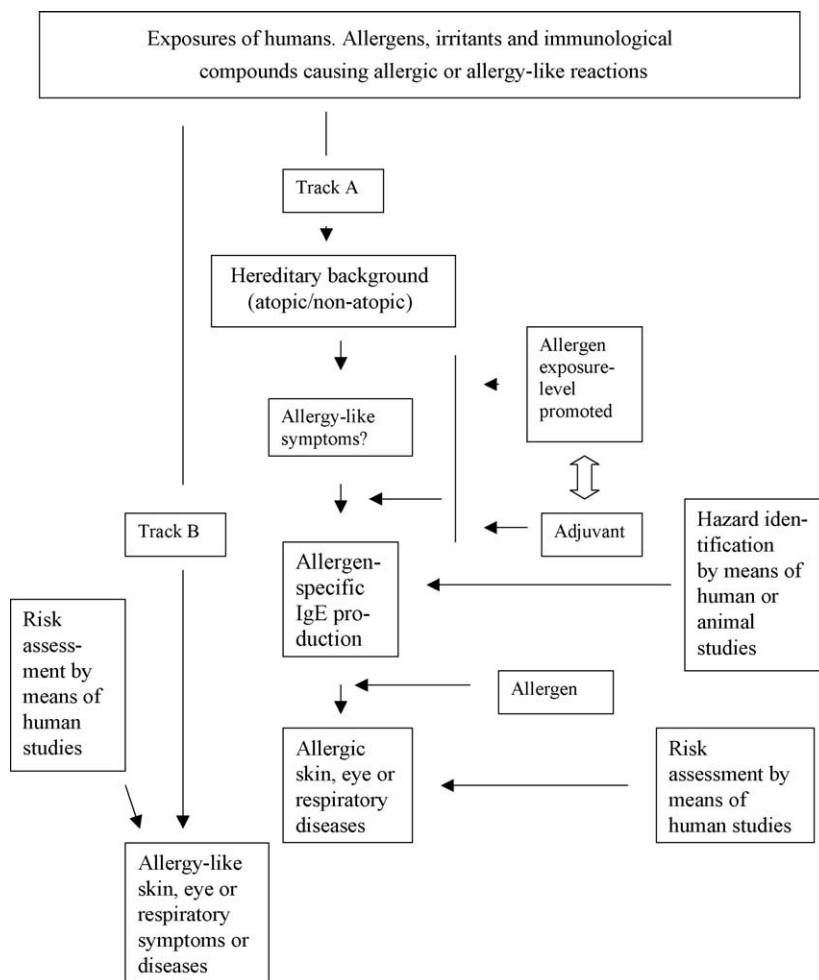


Fig. 1. Proposal for a general model for hazard identification and risk assessment of adjuvant effects of environmental exposures based on experiences from smoking and occupational exposures to high molecular weight immunogens and haptens.

levels, airway inflammation and asthma (Barnes, 2000; Bracken et al., 2002). This review indicates that atopy may play a role in sensitisation and allergic reactions with allergens from green coffee and castor beans, flour dust, latex, laboratory animal and seafood exposures, but has a limited or no effect with exposures to enzymes, platinum salt, acid anhydrides and reactive dyes. Overall, the relevant allergen or hapten strongly influence whether or not hereditary predisposition leads to sensitisation.

In the model (Fig. 1), smoking is considered a modifying factor in relation to IgE-mediated sensitisation and development of airway diseases, as smoking showed adjuvant effect in relation to exposures to green coffee and castor beans, seafood, enzymes, platinum salts and reactive dyes. Occasionally, an adjuvant effect was seen in exposures to acid anhydrides and the pharmaceutical

products, ispaghula, senna and psyllium. No clear adjuvant effect appeared from exposures to flour and grain dust, latex and laboratory animals. Overall this suggests that effects of adjuvants are strongly dependent on the co-exposed allergen.

There are several limitations in establishing a model for evaluation of adjuvant effects from occupational allergen exposures and smoking, although the occupational exposures constitute one of the most comprehensive databases, with relatively well characterized allergen exposures. The epidemiological studies may cause overestimation as well as masking of adjuvant effects.

Underestimation of negative studies may have occurred in our analysis, as studies reporting in qualitative terms (e.g. "smoking was not associated with any outcomes") have been excluded if it was not possible to identify what was studied in relation to a specific

immunological endpoint. Positive results may have been reported more in depth, which may tend to overestimate the importance of smoking.

Exposures need not be well defined and comparable, which may apply both to smoking and to the seemingly similar types of occupational exposure. For example, smokers may use low or high-tar cigarettes and may smoke more or less, which may influence immunological endpoints (Johnson et al., 1990). This may have contributed to some of the non-concordant results and may hamper the use of meta-analyses.

Detection of sensitisation depends on the ability of the reagents used to detect skin reactions or to detect specific IgE antibodies, as apparent from studies in seafood workers (Cartier et al., 1986) and thus may also have influenced the estimates. Also, different types of diseases and exposures may cause similar clinical symptoms. Wheezing may be due to asthma, but also to airway infection and bronchitis (Charpin et al., 1988).

From studies in bakers (Baur et al., 1998) and workers exposed to grain dust (Baur et al., 2003), it was apparent that rhinitis and asthma symptoms were due both to IgE and non-IgE-mediated reactions, which applies to many other types of organic dust (Rylander, 2004). The non-IgE-mediated reactions may, for example, be due to exposures to irritants and microbial products (Baur et al., 1998, 2003; Rylander, 2004). Similarly, non-IgE-mediated reactions could occur with exposures to organic acid anhydrides (Baur et al., 1995) and reactive dyes (Park et al., 1991). Thus, non-IgE-mediated reactions may influence detection of an adjuvant effect on the IgE-mediated processes. This has been included in the overall model (Fig. 1), which outlines general tracks of allergic sensitisation and diseases (track A) and non-IgE-mediated reactions (track B) with similar symptoms.

Also, the univariate analyses used for quantification of effects of smoking may result in groups, which are not comparable in other parameters, for example, age, sex and length of exposures, indicating that estimates should be taken cautiously.

9. Conclusions

The adjuvant effects of smoking ranged from having no role to having a very important role in sensitisation and development of allergic airway diseases. This applied both to atopic and non-atopic groups. The sensitisation stage is attractive for hazard identification of adjuvant effect both in human and animal studies. It can be measured objectively (at least theoretically) and in general more individuals are sensitised than indi-

viduals having developed allergic diseases. Also, the disease stage may be influenced by non-IgE-mediated reactions. From the many non-concordant results, it is apparent that risk assessment may be a complicated process, which at present is only accessible from epidemiological studies. As epidemiological studies may be influenced by other factors than allergen and adjuvant exposures, results should be compared with hazards identified in animal models to support cause–effect relationships. Development and use of appropriate animal models for risk assessment could be a strong supplement to epidemiological studies. However, it is apparent from the epidemiological studies that such models need to take hereditary effects, types of allergen, and exposure levels for allergens and adjuvants into account.

Acknowledgment

This study was funded by the Danish Environmental Protection Agency.

Appendix A

In a cohort study of N individuals in a given workplace (“population”), appearance of new cases (a and c) can be observed to belong either to the exposed ($a + b$) or the non-exposed ($c + d$) individuals of the population. The incidence and the incidence rate can be obtained from the four-fold table.

Reaction/disease				Incidence	Incidence rate
Exposure	+	–			
	a	b	$a + b$	$a/(a + b)$	$a/\text{person-year}(a + b)$
	–	c	d	$c/(c + d)$	$c/\text{person-year}(c + d)$
	$a + c$	$b + d$	$N = a + b + c + d$		

If available in the reference, the relative risk (RR) was obtained from the incidence rate ratio ($[a/\text{person-year}(a + b)]/[c/\text{person-year}(c + d)]$). If not, we estimated the RR from the incidence ratio (proportion), $(a/(a + b))/(c/(c + d))$ (Walter, 1978). The population-attributable risk (AR) may be defined as the proportion of disease that could be eliminated if exposure could be totally removed from the population and if the exposure is causally related to the disease (Walter, 1978). It may be calculated from the relation (Walter, 1978):

$$AR = \frac{Pe \cdot (RR - 1)}{[Pe \cdot (RR - 1) + 1]} \quad (1)$$

where P_e is the proportion of exposed, which corresponds to $P_e = (a + b)/N$ in the four-fold table. Finally, $AR(\%) = AR \cdot 100$.

In a cross-sectional study, the prevalence is obtained from the fraction of existing cases in the exposed and the unexposed part of the population. The prevalence ratio is preferred for the RR estimate (Thompson et al., 1998) and is calculated as for the incidence ratio, $RR = (a/(a + b))/(c/(c + d))$, using the terminology from the four-fold table. The AR is obtained from Eq. (1).

χ^2 -Tests were used to test the significance of four-fold tables from cohort and cross-sectional studies, where each cell contains five or more outcomes. If less than 5, Fisher's exact test was used.

Case-control studies were also analysed from a four-fold table (Walter, 1978).

		Cases	Control
Exposure	+	a	c
	–	b	d
		a + b	c + d

The preferred estimate of RR in case-control studies is from the odds ratio (Pearce, 2004), which is $OR = [a/b]/[c/d]$, and the $RR = (OR - 1)/OR$. The 95% confidence interval for the OR was used for testing of significance. The population-attributable risk is obtained from:

$$PAR = \frac{Po \cdot (OR - 1)}{[Po \cdot (OR - 1) + 1]}$$

where P_o is the proportion of exposed controls, which is $P_o = c/c + d$ in the latter four-fold table.

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