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Aetiological agents in occupational asthma

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ABSTRACT: Occupational asthma has become the most prevalent occupational lung disease in developed countries. At present, about 200 agents have been implicated in causing occupational asthma in the workplace. These agents can be divided into two categories by their mechanism of action: immunological and nonimmunological.

Immunological causes can be further divided into those that induce asthma through an immunoglobulin E (IgE)-dependent mechanism, and those that induce asthma through a non-IgE-dependent mechanism. In the latter category, specific IgE antibodies are found only in a small percentage of the patients with proven disease, even though the clinical picture is compatible with an allergic reaction. The immunological mechanism(s) responsible for these agents has yet to be identified.

The best known example of nonimmunological asthma is Reactive Airways Dysfunction Syndrome (RADS) or irritant-induced asthma.

In this review, examples of types of agents causing occupational asthma are discussed and a compendium table of aetiological agents is given.

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The prevalence of occupational asthma has increased over the past two decades [1, 2]. This due partly to a better recognition of the condition, and partly to an increase in the number of new chemicals capable of causing occupational asthma in the workplace. At present, nearly 200 agents have been implicated in causing occupational asthma in the workplace [3].

Definition of occupational asthma

In this article, occupational asthma is defined as recommended by BERNSTEIN *et al*. [4]. It is a disease characterized by variable airflow limitation and/or nonspecific bronchial hyperresponsiveness (NSBH) due to causes and conditions which are attributable to a particular occupational environment and not to stimuli encountered outside the workplace. Occupational asthma may encompass both immunological and nonimmunological causes 1) immunological occupational asthma occurs upon exposure to an agent after a latent period of immune sensitization; 2) nonimmunological asthma may or may not occur after a latency period of exposure to an agent(s) which does not induce immune sensitization as determined by currently available technology

Under certain exposure conditions, immunological and nonimmunological asthma may be concurrent.

Aetiological agents in occupational asthma

The aetiological causes of occupational asthma can be classified into immunological and nonimmunological. Immunological causes can be further divided into those that induce asthma through an immunoglobulin E (IgE)-dependent mechanism, and those that induce asthma through a non-IgE-dependent mechanism. In the latter category, specific IgE antibodies are found in only a small percentage of the patients with proven disease, even though the clinical picture is compatible with an allergic reaction. The immunological mechanism has yet to be identified. As it is not possible to cover all aetiological causes in this article because of limited space, only the most commonly encountered and most studied causes will be discussed.

Agents causing asthma through immunological mechanisms

Occupational asthma due to immunological causes has the following characteristics that distinguish it from occupational asthma due to nonimmunological causes: 1) there is a latent period between the onset of exposure and the onset of respiratory symptoms; and 2) in sensitized subjects, re-exposure to a small amount of the causative agent leads to the occurrence of asthma.

IgE-dependent causes

It has been demonstrated for many years that agents inducing asthma through an IgE-dependent mechanism are high molecular weight proteins or polysaccharides. Recently, several low molecular weight compounds have been shown to produce specific IgE antibodies, by

combining with a protein to form a hapten-protein conjugate [5]. There is good evidence to suggest that specific IgE antibodies to the hapten-protein conjugate are responsible for the patients' symptoms. Occupational asthma due to IgE-dependent aetiological agents mostly affects atopic subjects. In sensitized subjects with symptoms, specific inhalation challenge tests with extracts of these agents induced isolated immediate asthmatic reaction or a biphasic asthmatic reaction, but rarely an isolated late asthmatic reaction. Smoking has been shown by some to be an important determinant of some types of occupational asthma but not others [6]. Table 1 in the Appendix shows some of the IgE-dependent causes of occupational asthma, according to industries, jobs or work processes where the exposure can be found.

High Molecular weight compounds (table)

Animal products

Laboratory animal allergens. Exposure to laboratory animals occurs in the pharmaceutical industry, in university and research units, and in animal breeding facilities. Small animals are often used in these places. The most common cause of asthma is rats, followed by mice, and rabbits. The allergens are usually found in the excreta and the secreta of these animals [7]. In rats and mice, the major source of allergen is in the alpha$_2$-globulin and/or the prealbumin portion of the protein in urine [7]. The allergenic protein appears in the urine of male rats after puberty and disappears with senility. In guinea-pigs, allergens have been identified in the urine, serum, saliva and pelt. Again the allergenic activity is highest in the prealbumin region. The nature and the sources of rabbit allergens have been less extensively studied.

The prevalence of asthma due to laboratory animal allergy is not know. In the United Kingdom, the Surveillance of Work-Related and Occupational Respiratory Disease (SWORD) project group [1] reported an estimated incidence of 204 cases of occupational asthma per million animal handlers per year. About one third of the animal handlers have allergic symptoms, such as allergic rhinitis and contact urticaria; whilst 10% have symptoms of asthma. The results of a longitudinal study of workers in the pharmaceutical industry were reported by BOTHAM *et al.* [8]. The prevalence of specific IgE antibodies to rat urine proteins was 28% during the first year of employment, 37% in the subsequent two years, but fell to around 10% in the fifth to seventh year [8]. The improvement was attributed to improved work practice and the use of personal protection rather than to selection.

Clinically, allergic symptoms develop within the first 2–3 yrs of exposure. A recent study of patients with different types of occupational asthma showed that the latency period between the onset of exposure and the onset of symptoms is longer for patients with asthma due to high molecular weight compounds than for those with asthma due to low molecular weight compounds [9]. Asthma usually occurs several months after the development of other symptoms. Atopic animal handlers are more prone to develop asthma [10].

The diagnosis of occupational asthma in laboratory animal handlers is based on the presence of a compatible history, with objective evidence of work relationship and evidence of sensitization. Objective evidence of work relationship can be obtained by peak expiratory flow rate (PEFR) monitoring for a period at work and a period off-work, or by a specific inhalation challenge test with appropriate extracts if available. Evidence of sensitization can also be obtained by a positive skin test or presence of specific IgE antibodies with the appropriate extracts.

One of the important technological advances in occupational asthma is the ability to measure the amount of airborne allergens [11]. This enabled investigators to study factors that determine the levels of allergens in animal laboratories and methods of reducing these allergens [12–14]. The latter includes the reduction of stock density, the use of female rats rather than male rats, the use of corn cob rather than wood shaving as bedding, and covering of the cages with filter caps [13].

Other animal-derived allergens. Other animal-derived proteins have been incriminated as causing occupational asthma. Asthma caused by exposure to pig-derived allergens in a meat factory has been described [15]. Handling of bovine serum albumin powder caused occupational asthma in a laboratory technician [16]. Exposure to egg proteins has been reported to cause occupational asthma [17]. In a survey of 188 workers employed in a factory that produced liquid and powdered egg products, 7% were found to have physician-diagnosed asthma and evidence of sensitization to one or more egg proteins [18].

Different types of insects can give rise to occupational asthma. Storage mites have been incriminated as allergens for occupational asthma among farmers [19, 20]. Other types of mites such as spider mites and poultry mites have been found to be the cause of occupational asthma in greenhouse workers and poultry workers, respectively, [21, 22]. Laboratory workers breeding insects such as grain weevil [23], locust [24, 25] and fruit fly [26], are at risk of developing occupational asthma.

Plant proteins of polysaccharides

Flour. In some countries, baker's asthma is the most prevalent type of occupational asthma [27]. The majority of patients with baker's asthma are allergic to wheat and rye flour. There is considerable cross-reactivity between antigens in wheat and rye flour and those in other cereals, such as barley and triticale, but less to oats, corn and rice [28]. Crossed immunoelectrophoresis studies of wheat extract identified 40 different allergens [29]. However, the major allergens are found in globulin, gliadin and glutenin fractions [30].

Several other non-cereal antigens have been identified as capable of causing asthma in bakers. Sensitization to

Aspergillus and Alternaria has been implicated in two bakers with asthma [31]. Other food additives such as alpha-amylase, hemicellulase and papain, used as enzymes in bakeries, can also cause sensitization [32, 33].

It has been estimated that about 10–20% of bakers suffer from baker's asthma [27]. A cross-sectional study of 318 bakers showed that 13% had respiratory work-related symptoms [34]. The degree of nonspecific bronchial hyperresponsiveness (NSBH), lung function level, and skin test reactivity to antigens tested correlated with the current level of flour dust exposure and the estimated total exposure.

The onset of asthma in bakers is usually preceded by nasal symptoms, such as sneezing, rhinorrhoea and itchy eyes. The latent period between the onset of exposure and the onset of respiratory symptoms varies between a few months and a few years [35]. Almost all patients are atopic subjects with skin reactivity to common allergens. The diagnosis of baker's asthma is usually based on a compatible clinical history, presence of airflow limitation and/or presence of NSBH, or the demonstration of positive skin test to the appropriate flour extract. Positive bronchial reactions to flour extract occurred in symptomatic workers in association with high specific IgE level and a higher degree of NSBH [36].

Workers exposed to grain dust such as grain elevator terminal workers and farmers do not, as a rule, become sensitized to cereal flours but to other components in the grain dust. For example, occupational asthma in grain farmers is usually related to sensitization to storage mites such as *Glycyphagus destructor* [37].

Pharmaceutical products. Some pharmaceutical products are proteins, such a ipecacuanha, derived from the roots of *Cephaelis ipecacuanha*, or polysaccharides, such as psyllium.

Occupational asthma due to psyllium has been studied more extensively than other proteinaceous pharmace utical products [38]. The clinical picture of psyllium-induced asthma is well-documented in several case reports [39–44]. In addition to asthma, many patients also complained of ocular and nasal symptoms [45]. Specific IgE antibodies to psyllium have been found in these patients. The prevalence of sensitization among pharmaceutical workers was between 28% [46] and 44% [47]; whilst the prevalence of occupational asthma confirmed by specific challenge test was 4% [46]. Among nurses working in long-term care facilities, the prevalence of positive skin test was lower (5%), but the prevalence of confirmed occupational asthma by specific challenge test was also 4% [38].

Gums. Gums are derived from plants and are high polymer carbohydrates that produce mucilages when they react with water. Common examples include acacia or arabic gum, used in the food and pharmaceutical industries; tragacanth, used mainly in printing; karaya, which grows in India, and can be used instead of tragacanth. Guar gum, another natural gum, was reported to be responsible for asthma in the carpet-manufacturing industry [48]. Occupational asthma due to acacia gum was described as early as 1933 [49]. Later, cases of asthma among printers exposed to acacia gums were documented [50]. Five percent of workers in a carpet-manufacturing factory was found to have positive skin tests to guar gum, while 2% had occupational asthma diagnosed by specific challenge tests [48].

Enzymes

Detergent enzymes. Proteolytic enzymes from *Bacillus subtilis* were introduced in detergent products in the 1960s. Within a few years of their introduction, several investigators reported the association of exposure to detergent enzymes with asthma, nasal and ocular symptoms among workers involved in the manufacture of detergents [51, 52]. These workers showed positive skin test reactivity to *B. subtilis* alcalase and developed an immediate or late asthmatic reaction on inhalation challenge [53]. A fall in diffusing capacity was found in some workers following inhalation challenge test, suggesting involvement of lung parenchyma as well as airways [52]. An epidemiological study of detergent manufacturing workers demonstrated that 21% had skin sensitivity to alcalase; of these, 66% were atopic subjects [54]. Reports of sensitization in consumers followed later. Four percent of 461 individuals attending an allergy clinic with no known occupational exposure to detergent enzymes had positive skin test to alcalase [53]. Positive nasal or bronchial reactions to challenge with the enzyme were documented in some of the consumers [53].

Since these reports, measures were taken to reduce exposure not only for workers but also consumers. Ventilation was improved in factories, and changes were made in manufacturing processes, such as enclosing the purification of enzymes. These enzymes were also glued to phosphate granules to prevent them from getting dispersed, or were encapsulated. Despite the substantial reduction in levels, a study showed that sensitization still occurred in 25% of workers [55]. However, in a study of the general population, no sensitization to alcalase was found, indicating that the use of enzymes in granules and encapsulation had been successful, at least in eradicating the disease among consumers [56].

Other enzymes. Both plant-derived enzymes, such as papain from papaya and bromelin from pineapple, and animal-derived enzymes, such as hog trypsin, are frequently used in the food industries. Some of them have been found to cause occupational asthma [57].

Fish and seafood protein

Processing of several types of seafood can cause occupational asthma. Oyster handlers were found to be sensitized to the "hoya" or "sea-squirt" contaminating oysters, and developed symptoms of rhinitis and asthma [58]. Oysters themselves were not the source of allergen. Processing of prawns gave rise to asthma in 18 out of 50 workers [59]. Inhalation challenge test with the

prawn extract on two volunteers induced isolated late asthmatic reaction in one and dual asthmatic reaction in the other [59].

Occupational asthma associated with snow crab processing has been studied in detail [60]. During the process of boiling, a vapour is released from the snow crab. Inhalation of the vapour containing proteins from snow crabs resulted in sensitization of workers. In a study of two snow crab processing plants along the St. Lawrence River with 313 employees, 33 were confirmed to have occupational asthma by specific challenge tests [60].

Low molecular weight compounds (table 1)

Some low molecular weight compounds have been shown to cause occupational asthma associated with the production of specific IgE antibodies against the hapten-protein conjugates. The most well known compounds in this group include acid anhydrides, metals such as platinum and some pharmaceutical products.

Acid anhydrides

There are several acid anhydrides: phthalic anhydride, trimellitic anhydride, hexahydrophthalic anhydride, himic anhydride and tetrachlorophthalic anhydride. These anhydrides are used in alkyd and epoxy resins. Alkyd resins form the base for paints, varnishes and plastics. Epoxy resins are widely-used in adhesives, casting, coating, and sealants. Trimellitic anhydrides are mainly used as plasticizers for polyvinyl chloride, especially when temperature stability is required. Acid anhydrides can give rise to hypersensitivity reactions in exposed population. They act as haptens and combine with proteins to form conjugates with antibodies recognizing the haptens [61]. They can also combine with self-proteins to generate new, carrier-dependent antigenic determinants with antibody combining sites being directed against a conformational change in the self-proteins [61].

Phthalic anhydride. Since 1939, phthalic anhydride has been known to cause asthma and rhinitis [62]. Specific IgE antibodies to phthalic anhydride conjugated to human serum albumin have been demonstrated [63].

Trimellitic anhydride. Trimellitic anhydride induced not only specific immunoglobulin E, A, M and G (IgE, IgA, IgM and IgG) antibodies against the hapten but also to the new antigenic determinants that arise when trimellitic anhydride couples with proteins [61]. Trimellitic anhydride has been shown to cause a spectrum of lung diseases: asthma and rhinitis, late respiratory systemic syndrome and pulmonary disease-anaemia syndrome [64]. Whilst IgE antibodies are probably responsible for asthma, connections have been made between other antibodies and late respiratory systemic syndrome and pulmonary disease-anaemia syndrome [65]. A study was conducted on 474 employees exposed to trimellitic anhydride. Evidence of trimellitic anhydride immunological lung disease was observed in 6.8% [66]. A direct relationship was found between the levels of total and IgE antibodies and the degree of exposure.

Tetrachlorophthalate anhydride. In a survey of 276 workers exposed to tetrachlorophthalate anhydride (TCPA), specific IgE antibodies to the TCPA-conjugate were found in 12% of atopic subjects and 6% of nonatopic subjects. There was a strong interaction between smoking and atopy; smokers who were atopic subjects had the highest prevalence of positive specific IgE antibodies [67]. A follow-up study of workers with TCPA-induced asthma showed a progressive reduction in levels of specific IgE antibodies after removal from exposure. The half-life of these antibodies was one year [68]. Various animals: rats, Rhesus monkeys, dogs, rabbits and guinea-pigs have been used, without success, to induce a model of IgE-mediated airway disease to anhydrides [61]. Although other types of hypersensitivity reactions were induced, airway hyperresponsiveness was not found.

Metals

In addition to asthma, inhalation of metallic compounds can give rise to chemical pneumonitis, bronchitis and metal fume fever. Chronic exposure has been associated with chronic bronchitis, emphysema and, in the case of hard metals, pneumoconiosis.

Exposure to metals may occur not only in metal mining and metallurgical industries, but in a number of other trades, such as welding and soldering. Chromates are found in paints, chemical and plastic industries, while cobalt is found in diamond polishing discs [69]. Metals that can induce asthma can be divided into three categories: 1) transition metals, such as vanadium, chromium, nickel and zinc; 2) precious metals, such as platinum and palladium; and 3) hard metals, such as tungsten carbide and cobalt.

Nickel. Exposure to nickel occurs during mining, milling, smelting, and refining processes, as well as in electroplating industries and in the production of nickel catalysts. The occurrence of nickel-induced asthma among exposed workers is rare compared to contact dermatitis. In the literature, there have been several case reports of nickel-induced asthma associated with exposure to nickel sulphate; some confirmed by inhalation challenge tests [70, 71]. Specific IgE antibodies to nickel-human serum albumin conjugate have been reported in some cases [70]. Recently, lymphocyte transformation was demonstrated in patients with nickel-induced asthma, suggesting that cell-mediated hypersensitivity may play a part in nickel-induced asthma [72].

Chromium. Chromium metal is nonallergenic. Chromium salts are well-known to give rise to contact dermatitis. Exposure to chromium salts occurs in electroplating, tanning, pigment and cement production. The development of asthma is frequently preceded by a history of

contact dermatitis. As in nickel-induced asthma, cell-mediated hypersensitivity may be important.

Platinum. Platinum salts, particularly halides, are more potent in inducing asthma than other metallic salts. Exposure to platinum occurs in mining, in primary and secondary refining processes, and in chemical industries where platinum is used as a catalyst. During the refining process, hydrochloric acid and chlorine are added. It is the halide salts that give platinum its allergenicity. Platinum-induced asthma has been recognized for a long time [73, 74]. Positive skin tests with the appropriate platinum salts (unconjugated) were found in sensitized workers [75]. Specific IgE antibodies were detected by radio allergosorbent test (RAST) procedures [76]. A Type I allergic reaction is likely to be responsible for the pathogenesis of platinum salt-induced asthma.

In a recent cross-sectional study of a secondary refinery, 14% of the 107 current employees and 28% of the 29 workers laid-off for medical reasons had positive skin test reactivity to platinum salts, suggesting that the current employees were "healthier". In this study, the prevalence of atopy was similar among those with positive and negative skin tests to platinum salts, and those of the general population, suggesting that atopy is not an important determinant. However, smoking was found to be strongly associated with sensitization to platinum salts [77].

Zinc. Exposure to zinc occurs in the steel manufacturing industry, where it is used as an alloy. It is also used as a component of brass, and in the insecticide industry. The most important exposure to zinc occurs in welding of galvanized iron. Exposure to fumes of zinc oxide is associated with metal fume fever, which is a flu-like illness, sometimes associated with cough and shortness of breath. Several cases of occupational asthma have been described related to exposure to fumes of zinc oxide [78, 79].

Other

There are other low molecular weight compounds that can act as haptens and cause asthma by inducing specific IgE antibodies. It is not possible to discuss all of them here.

Non-IgE-dependent causes

The majority of low molecular weight compounds induce asthma by mechanisms as yet unidentified, as specific IgE antibodies to the offending agents have not been found, or found in only a small proportion of patients with the disease. The clinical picture of these patients is compatible with that of an allergic disease. The accompanying table shows some of these causes. Specific challenge tests with these agents commonly induce late asthmatic reactions, either as an isolated asthmatic reaction or as the late component of biphasic reactions, and in some cases reactions that are atypical [80]. The majority of affected subjects are nonatopic and nonsmokers [81]. Thus, these non-IgE-dependent agents are different from other types of low molecular weight compounds that induce specific IgE antibody production. Asthma due to diisocyanates and asthma due to the Western red cedar are examples of non-IgE-dependent causes that have been studied in detail and will be discussed here.

Diisocyantes

Occupational asthma due to diisocyanates has been reviewed in detail by VANDENPLAS *et al*. [82]. Diisocyanates are being used extensively in a number of important industries all over the world. They are a group of small molecular weight cyclic or linear organic chemical compounds, synthesized by the reaction of amines or their hydrochlorides with phosgene. These chemicals all have an -N=C=O group attached to a radical, and react exothermically with compounds containing active hydrogen atoms, such as polygycols, to form a polymeric mass, polyurethane (fig. 1). Monomers of isocyanates can exist in aromatic, aliphatic or cycloaliphatic forms (fig. 2). Prepolymers of isocyanates have also been shown to give rise to occupational asthma [82]. Toluene diisocyanate (TDI) was first developed during the second World War and is the most commonly used diisocyanate. Since that time, other isocyanates have been developed, such as methylene diphenyl diisocyanate (MDI), hexamethylene diisocyanate (HDI), naphthylene diisocyanate (NDI), and isophorone diisocyanate (IPDI). They are used in the production of rigid and flexible foams, as protective coatings for electric wiring, for painting automobiles, as adhesives and binders in foundries, as liners for mine and grain elevator chutes, soles of shoes and spandex fibres. Thus, they have a wide application in both industrial and domestic use.

Toluene diisocyanate. TDI-induced asthma has been the most common cause of occupational asthma in many parts of the world for many years. However, in recent years, it has been replaced by HDI and MDI [82]. The prevalence of TDI-induced asthma varies from 5 to 10%, depending on the type of industry, the type of diisocyanate, and the level of exposure [82]. Many cases of TDI-induced asthma occurred after a high level of exposure, *e.g*., a spill [83]. In those situations, a Reactive Airways

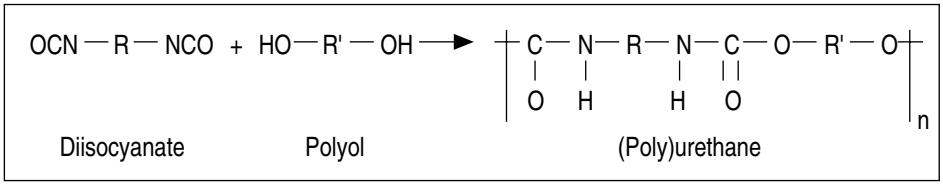

Fig. 1. – -N=C=O) group attached to a radical, reacts with compounds containing active hydrogen atoms, such as polyglycols, to form a polymeric mass, polyurethane.

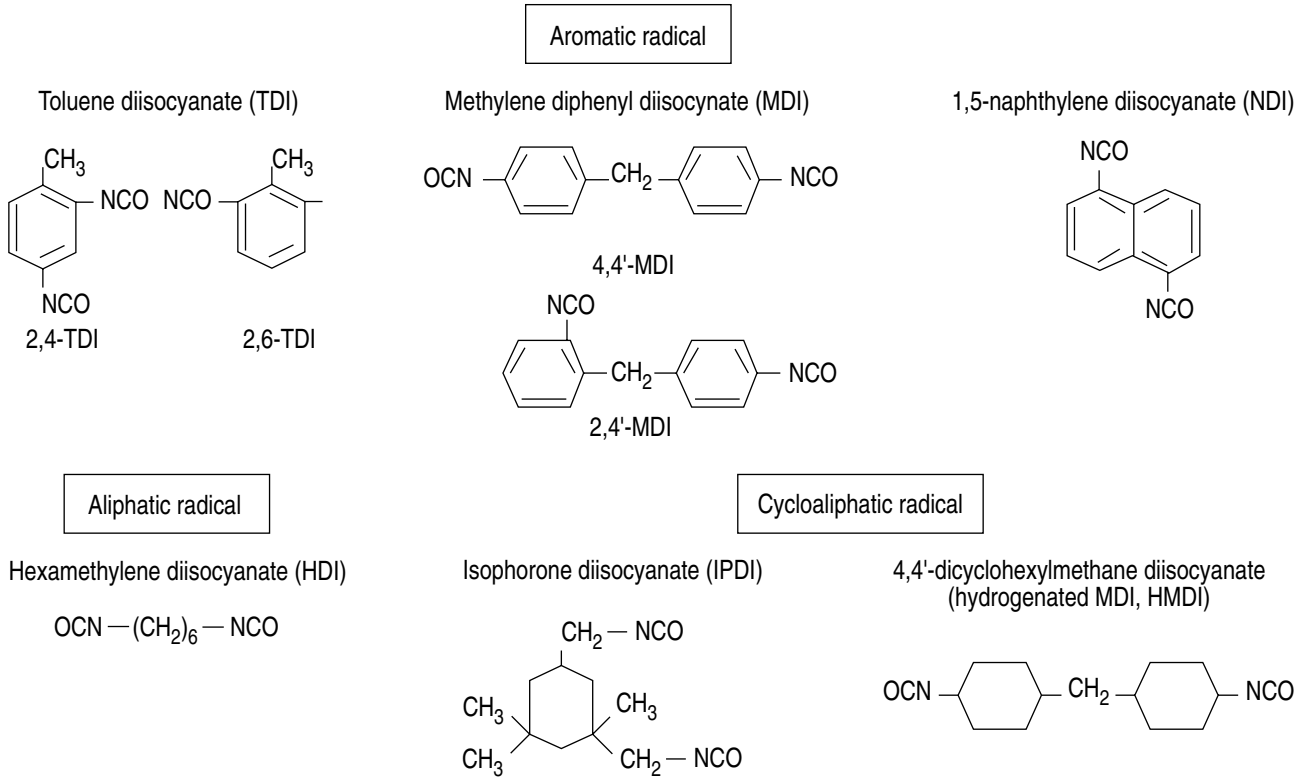

Fig. 2. – Structure of different monomers of isocyanates.

Dysfunction Syndrome (RADS)-type of occupational asthma could not be excluded. Recently, there has been a report that certain genetic factors related to human leucocyte antigen (HLA) Class II may convey protection, whilst others convey susceptibility [84]. Obviously, a great deal of work needs to be done in this area.

The dose and length of exposure to TDI which will induce asthma are not known. Recommendations from the National Institute for Occupational Safety and Health (NIOSH) are that humans should not be exposed to concentrations above 20 ppb [85]. Several animal models have been developed to study TDI hypersensitivity reaction. In guinea pigs, specific IgG_1 and not IgE antibodies were found; in another study, specific IgE antibodies were detected [86, 87]. Irrespective of whether antibodies were present or not, the animals developed airflow obstruction and NSBH. The uptake and distribution of TDI have also been studied in guinea-pigs [88, 89]. Most of the TDI was absorbed in the upper airways; the uptake, as reflected by the concentration of ^{14}C in the blood, correlated with the concentration in inhaled air. In the airways, labelled TDI was found in the epithelium and subepithelium from the nose to terminal bronchioles but not in the alveoli [88, 89]. In the blood, the labelled TDI was found in the plasma, conjugated to a 70,000 kD a molecular weight protein. In the airways, TDI was also found conjugated with a 70,000 kD a molecular weight protein, which was shown to be laminin. These studies may be helpful for the identification of the protein conjugated to isocyanates in humans.

Clinically, once a subject has been sensitized to TDI, very low levels of TDI (as low as 1 ppb) may trigger an attack of asthma. Specific challenge tests with TDI-induced isolated immediate, isolated late, biphasic or a continuous reaction in sensitive subjects. Recurrent late asthmatic reaction has been reported after one single challenge to TDI [90]. The development of late asthmatic reaction has been shown to be accompanied by the development of NSBH in about 60% of subjects [80]. Once asthma has developed, the majority had persistence of symptoms even after they were removed from exposure [91–94]. Favourable prognostic factors include early diagnosis and early removal from exposure. The mechanism of TDI-induced asthma is not known. Specific IgE antibodies to a protein conjugate of TDI or a monoisocyanate were present in only a small proportion (10–20%) of patients who were shown to have specific asthmatic reactions on inhalation challenge test. Skin prick testing with hapten-protein conjugates has been negative [95]. There have been reports indicating that the immune response could be directed against neoantigens formed by the reaction of TDI with body proteins [96], as in other highly reactive low molecular weight compounds [97]. Specific lymphocyte blastogenic activity and lymphokine leucocyte inhibitory factor responses to TDI have been detected in sensitive workers, and suggest that cell-mediated hypersensitivity reaction may play a part [96]. TDI has several other effects that might induce NSBH or potentiate sensitizing properties. It has been shown to have beta-adrenergic blockade properties [98], to stimulate the release of neuropeptides and to inhibit neutral endopeptidases in *in vivo* and *in vitro* studies [99].

Irrespective of the mechanism of induction of asthma, airway inflammation was found in patients with TDI-induced asthma both by bronchoalveolar lavage (BAL) and bronchial biopsy studies [99]. The pathology of the lungs of a patient with isocyanate-induced asthma who died during an attack showed similar findings as those

who died from status asthmaticus [100]. The airways were plugged with mucus. There was sloughing of the epithelium and marked cellular infiltration of neutrophils and eosinophils. The basement membrane was thickened and the smooth muscle hypertrophied. The pathology of the airways of patients with TDI asthma was studied before and after exposure ceased. The thickening of the basement membrane observed when the patients were still exposed and symptomatic became less severe, suggesting this change was partly reversible [99].

Methylene diphenyl diisocyanate (MDI)

Methylene diphenyl diisocyanate is used in the production of rigid foam, and as a binder in almost all mould and core processes in iron and steel foundries. At room temperature, MDI is a solid. It has to be heated above 60°C before vapours are given off. The health effects of MDI exposure are less well-studied than TDI. Both occupational asthma and hypersensitivity pneumonitis and a combination of both have been described [82]. The prevalence of these diseases among exposed workers is not known. In one study of 78 workers in an iron and steel foundry utilizing MDI as a binder, the prevalence of cough, wheeze and chest tightness associated with NSBH was 18% [101]. A specific challenge test with MDI on 11 of the workers showed that six had a specific asthmatic reaction, two had a dual reaction, and four had an isolated late reaction. Four out of the six workers had recurrent nocturnal asthmatic reaction after one challenge test. Both specific IgE and specific IgG antibodies to MDI-HSA conjugate were detected in workers exposed to MDI. The relationship between the clinical disease and the presence of antibodies is not clear in MDI-induced asthma. At this stage, the presence of antibodies should indicate the presence of sensitization and not necessarily disease. In MDI lnduced hypersensitivity pneumonitis, however, specific IgE or IgG antibodies are usually present [102].

Hexamethylene diisocyanate (HDI). Hexamethylene diisocyanate is more volatile than TDI but it is used extensively in automobile and aircraft spray paints to produce finishing coatings. Cases of occupational asthma due to HDI exposure have been reported in the literature [82]. A prospective study was carried out on 150 workers exposed to HDI and its trimer during an 18 month period [103]. Specific IgE and IgG antibodies to a protein conjugate were detected in 21% of the workers. The presence of antibodies was not associated with the presence of clinical disease. However, the duration of follow-up was short, and it was not possible to draw any firm conclusions.

Western red cedar

Occupational asthma due to Western red cedar dust exposure is the most common type of occupational asthma in the Pacific Northwest. In British Columbia, Canada, it accounts for 70% of all the compensation claims for occupational asthma (Chan-Yeung M, unpublished observation). Western red cedar is used extensively for both indoor and outdoor construction, because of the durability. It is different from other wood in its high content of chemicals in the wood. Plicatic acid (PA) is one of the chemicals present uniquely in this wood and it has been found to be responsible for red cedar asthma [104]. Its structural formula is shown in figure 3. It has a molecular weight of 440 Da.

Red cedar asthma affects 4–14% of the exposed population, depending on the type of industry and the level of dust exposure [105]. There is a good correlation between the dust level and the prevalence of work-related asthma in exposed workers [106, 107]. The higher the dust concentration, the higher the prevalence of work-related asthma. As in TDI-induced asthma, the patients are mostly nonatopic subjects and nonsmokers. Recently, a follow up study of workers in a cedar sawmill showed that NSBH only developed in parallel with the development of red cedar asthma, indicating that NSBH is not a predisposing host factor [108].

The clinical feature of red cedar asthma is similar to TDI-induced asthma. There is a latent period between the onset of exposure and the onset of symptoms. At the onset of the disease, the patients usually complain of cough, wheeze, and shortness of breath at the end of the workshift. Later, with continual exposure, the patients complain of symptoms immediately they are exposed to the wood dust. In the first stages of illness, there is a remission of symptoms during weekends and holidays. Later on, there is no remission of symptoms. Inhalation challenge test with an extract of Western red cedar or plicatic acid induce the same types of asthmatic reactions as patients with TDI. Systemic reaction or alveolar reaction has not been observed.

Follow-up studies of patients with red cedar asthma showed that about 60% of patients failed to recover several years after they were removed from exposure [105]. Those who recovered, tended to be diagnosed early and removed from exposure early. They had normal lung function and a lower degree of NSBH at the time of diagnosis compared to those who failed to recover. For those who had to remain in the same job, persistent asthma was the rule. The use of respirators and the reduction of exposure by a change to a less dusty job did not improve the prognosis [109].

The pathogenic mechanism of asthma induced by PA is not clear. Skin tests with extracts of red cedar and PA have been negative in patients with proven disease [104]. Plicatic acid can be conjugated to human serum albumin (HSA) to form an allergen. Using this conjugate as antigen, specific IgE antibodies can be found by radioallergosorbent tests (RASTs) method in about 20% of patients proven by inhalation challenge [110]. Bronchoalveolar lavage studies of patients before and during immediate asthmatic reaction showed a release of inflammatory mediators, including histamine, prostaglandin D_2, leukotriene E_4 and thromboxane B_2 into the BAL fluid [111]. During the late reaction, an increase in eosinophils and albumin was found, together with sloughing of the epithelium [112]. Bronchial biopsy performed during

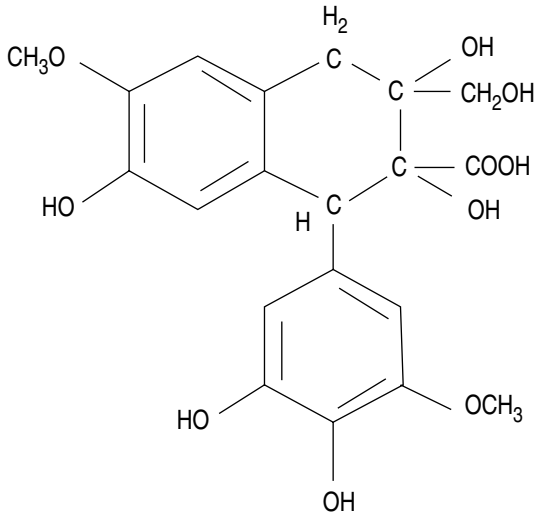

Fig. 3. – Structure of plicatic acid.

the late reaction showed similar findings to patients with allergen-induced asthma [112]. These findings suggest that there might be low levels of specific IgE antibodies to PA-HSA conjugate, not detectable by the RAST method.

To test the above possibility, serum from patients with red cedar asthma was used to passively sensitize human lung fragments, and the fragments were then challenged with PA. No release of histamine was found, even though, under the same conditions, the lung fragments released histamine when passively sensitized and then challenged with grass pollen extract [113]. Basophils from patients with red cedar asthma were found to release histamine on direct challenge with PA. There was no inhibition of release of histamine when the basophils were previously desensitized by incubation with anti-IgE, while this desensitizing protocol reduced the responsiveness of basophils from atopic subjects to a challenge with grass pollen or with anti-IgE. These findings confirmed that specific IgE antibodies cannot be responsible for the release of histamine in patients with red cedar asthma. Further studies need to be carried out to clarify the pathogenic mechanism in red cedar asthma, as this may help us to understand the pathogenic mechanism of nonatopic or intrinsic asthma in general.

Amines

Various secondary, tertiary and quarternary amines, either aliphatic, heterocyclic or aromatic, have been reported to cause occupational asthma [114]. These chemicals are found in primary manufacturing and in secondary industries, such as the rubber, cosmetics, shellac, fur and hair dye industries, aluminium soldering, acrylate paint, and photography development [115].

Amines have been shown to cause occupational asthma in workers exposed to epoxy resins, which were produced by amines acting as cross-linking agents binding the resin molecules together [114]. Ethylenediamine caused occupational asthma in the beauty culture industry and among radiographers and photographers who develop films [115]. Another amine, piperazine, is used as an anthelminthic drug [116]. A survey of 131 workers exposed to piperazine and ethylenediamine revealed that 8% were asthmatic [117]. Specific IgE antibodies to piperazine-HSA conjugate were detected in five out of 72 exposed workers [117]. The mechanism by which amines cause asthma remains unclear.

Colophony and fluxes

Colophony is widely-used as a flux in electronic industries to prevent corrosion. It is obtained from pine trees containing abietic acid. The mechanism of occupational asthma due to colophony is not known at present. A specific challenge test induced isolated immediate, isolated late, or dual asthmatic reaction in sensitized subjects. In a survey of 446 electronic workers, a prevalence of work-related symptoms was found in 22% [118]. Atopy was a weak predisposing factor and smoking was not a determinant of work-related symptoms. There was a relationship between the degree of exposure and the prevalence of work-related symptoms. A follow-up study of 39 workers with asthma due to colophony exposure showed that symptoms persisted in half of them up to 4 yrs after exposure ceased [119].

Other soldering fluxes that can cause occupational asthma include zinc chloride and ammonium chloride [120], as well as one containing polyether alcohol-polypropylene glycol [121].

Pharmaceutical products

Whilst a number of pharmaceutical products have been shown to cause occupational asthma *via* an IgE-dependent mechanism, such as psyllium, ipecacuanha, pancreatic and glandular extracts, there are others that can cause occupational asthma *via* as yet unidentified mechanisms. These include several antibiotics, such as penicillins, amoxycillin, ampicillin, penicillamine, cephalosporins, phenyglycine acid chloride, and spiramycin [122]. Many of the cases were proven by specific challenge tests. Several nonantibiotic drugs can also cause occupational asthma, such as tylosin tartrate [123], alpha-methyldopa [124], amprolium hydrochloride [125], and morphine [126].

Miscellaneous

Exposure to many other chemical compounds in industries, such as chloramine T, a sterilizing agent used in the food and beverage industry [127], persulphate salts used among hairdressers [128], diazonium salts in photo-copying process [129], reactive dyes in textile industry [130] and azobisformamide in plastics industry can give rise to occupational asthma [131]. It will not be possible to discuss each one of them in detail. Readers should refer

to table 1 in the Appendix and the text book "Asthma in the Workplace" [3, 4].

Agents causing occupational asthma through nonimmunological mechanisms

Nonimmunological occupational asthma may or may not occur after a latency period of exposure to an agent(s) which does not induce immune sensitization as determined by currently available technology. The main distinction between this type of occupational asthma and immunologically-dependent ones is that in the majority of cases re-exposure of the affected subjects to small amounts of the offending agent does not reproduce the symptoms. Several types of occupational asthma belong to this category, and are described briefly below.

Reactive Airways Dysfunction Syndrome (RADS)

This syndrome was originally coined by BROOKS and co-workers [132] in 1985, to describe 10 subjects who developed symptoms of asthma and NSBH after one single exposure to high levels of an irritant vapour, fume or smoke. None of the subjects had a previous history of respiratory symptoms. Respiratory symptoms and NSBH persisted for about 3 yrs after the initial event. The incriminated exposure was either short-lived, often lasting just a few minutes or, on occasions, was as long as 12 h. There was a time interval between exposure and development of symptoms, varying from several minutes to several hours. The exposure was usually due to an accident or a situation where there was very poor ventilation and high exposure. Bronchial biopsies were performed on two cases. Whilst there was evidence of epithelial injury, with bronchial wall inflammation, the cells were lymphocytes and plasma cells; eosinophils were not found. In addition, there was no evidence of mucous gland hyperplasia, basement membrane thickening or smooth muscle hyperplasia. However, more recent biopsy data on subjects with this syndrome revealed typical histopathological features of asthma [133].

The incriminating agents were all irritants, including floor sealant, heated acid, fumigating fog, metal coating remover, acetic acid [134], smoke inhalation, TDI, and ammonia fumes [133].

Since re-exposure of these subjects to low levels of the incriminating agent did not reproduce symptoms, the diagnosis is a clinical one based on the history. The number of case reports is limited. The outcome of these subjects has not been as well documented as other types of occupational asthma. The syndrome needs to be studied in more detail to define it better.

Although BROOKS and co-workers [132] first coined this syndrome as RADS, there have been reports of persistent symptoms and a single, high concentration environmental or occupational irritant exposure. Five cases of accidental exposure to high levels of sulphur dioxide have been reported, with three survivors developing severe and another showing a mild degree of airflow obstruction [135]. A man aged 50 yrs developed obstructive airways disease after exposure to high concentration of ammonia vapours [136]. Several other studies of the sequelae of chlorine gas exposure showed similar findings [137, 138].

There are no data on the prevalence of this syndrome. The host risk factors are not known. A recent review of 59 consecutive cases of occupational asthma in the Toronto area in Canada showed that 17% were caused by exposure to irritants, suggesting that this syndrome is not that uncommon [139]. Longitudinal data are not available to indicate clearly that these subjects had no evidence of NSBH before the incident.

The pathogenesis of RADS is not clear. It has been postulated that the high level of exposure induces massive airway injury, followed by activation of non-adrenergic, noncholinergic (NANC) pathways *via* axon reflexes and the onset of neurogenic inflammation [133]. Nonspecific macrophage activation and mast cell degranulation may also occur, releasing proinflammatory mediators, with recruitment of inflammatory cells to the site of injury [133]. Epithelial injury has been shown to reduce the availability of an epithelial-derived relaxing factor and decrease neutral endopeptidase, leading to activation of the NANC nerves. As with other aspects of this syndrome, more research is necessary.

Potroom asthma

Potroom asthma has been reported among workers on potlines in aluminum smelting plants for many years [140]. Potroom workers are exposed to a number of contaminants, including particulate and gaseous fluoride, hydrofluoric acid, sulphur dioxide and hydrocarbons. The agent responsible for potroom asthma has not yet been identified. It has been postulated that the air contaminants in the potroom, if present in high concentrations, may induce asthma, as in RADS. The latent period between onset of exposure and the onset of symptoms varied from one week to 10 yrs [140]. Potroom asthma has been reported more frequently in smelters in Australia and Norway than in North America.

Machining fluid

Workers exposed to machining fluid can develop work-related asthma [141]. Machining fluids are contaminated with trace metals, additives such as antioxidants, detergents, anti-foam agents, and bactericidal agents. The latter are necessary to prevent the growth of bacteria and fungi. In addition to well-defined cases of asthma, cross-shift change in forced expiratory volume in one second (FEV_1) of less than 10% was reported in 24% of the heavily exposed and in 10% of the least exposed machinists [141]. The pathogenesis is not known, although the machining fluid is likely to act as an irritant.

Formaldehyde

Formaldehyde is an irritant at high concentrations, but a sensitizer in lower concentrations. Formaldehyde is

widely used in hospital environments, furniture manufacture and as insulation in buildings in the 1980s. In a prevalence study of 230 workers exposed to formaldehyde at work, 12 had significant bronchoconstriction at levels of 1–2 ppm during specific challenge tests [142]. Attempts to detect specific antibodies in the sera of workers exposed to formaldehyde have so far been unsuccessful [143].

Summary

This review gives a brief summary of the more commonly encountered aetiological causes of occupational asthma. Interested readers should refer to the textbook "Asthma in the Workplace" edited by BERNSTEIN *et al.* [4]. With the introduction of more chemicals into the workplace, the list is likely to increase. It should be emphasized that the absence of the suspected agent in any listing of aetiological causes of occupational asthma should not exclude the diagnosis. An international effort to prepare a data base similar to the Minitel System in France would be most helpful to clinicians and investigators in this field [144].

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Appendix

Table 1. – Selection of key references in occupational asthma (Reference list at end of table)

Agents	Occupation	[Ref]	Subjects n	Prevalence %	Skin test	Specific IgE	Other immunologic	Broncho-provocation test	Other evidence
High molecular weight agents									
Animal-derived antigens									
Laboratory animal	Laboratory workers	[1]	296	13	17% +	34% of 255 +	ND	ND	
		[2]	5	NA	100% +	100% +	Neg precipitin	100% +	
Cow dander	Agricultural workers	[3]	49	NA	100%	ND	Immunoblotting	ND	
Chicken	Poultry workers	[4, 5]	14	NA	79% +	79% +	ND	1/1+	
Pig	Butcher	[6]	1	NA	ND	+	ND	ND	+PEFR monitoring
Frog	Frog catcher	[7]	1	NA	+	+	Neg precipitin	ND	
Lactoserum	Dairy industry	[8]	1	NA	+	ND	+ basophil Degranulation	+	
Casein (cow's milk)	Tanner	[9]	1	NA	ND	+	ND	+	
Bat guano	Various	[10]	7	NA	+	+	RAST inhibition	ND	
Insects									
Grain mite	Farmers	[11]	290	12	21% +	19% of 219 +	ND	ND	
	Grain-store workers	[12]	133	33	25 +	23% of 128 +	ND	1/1 +	21% of 116 with + PC_{20}
Locust	Laboratory workers	[13]	118	26	32% of 113 +	Done	Specific IgG	ND	Reduced FEV_1
		[14]	15	60	77% +	53%	RAST inhibition	ND	
Screw worm fly	Flight crews	[15]	182	25	91% of 11 +	ND	ND	ND	
Cricket	Laboratory workers	[16]	2	NA	+	+	Passive transfer	+	
Bee moth	Fish bait breeder	[17]	1	NA	+	ND	Passive transfer Histamine release	ND +	
Moth, butterfly	Entomologists	[18]	2	NA	+	ND	ND	ND	
Mexican bean weevil	Seed house	[19]	2	NA	+	ND	Passive transfer	ND	
Fruit fly	Laboratory workers	[20]	22	32	27% +	27% +	RAST inhibition	21% of 14 +	
Honeybee	Honey processors	[21]	1	NA	+	+	ND	+	
L. caesar larvae	Anglers	[22]	5	NA	75% of 4 +	80% of 5 +	RAST inhibition	1/1 +	
Lesser mealworm	Grain and poultry workers	[23]	3	NA	Neg	100% of 3 +	RAST inhibition	ND	
Fowl mite	Poultry workers	[24]	13	NA	77% +	60%	ND	1/1 +	
Barn mite	Farmers	[25]	38	NA	100% +	~100%	ND	ND	
Mites and parasites	Flour handlers	[26]	12	NA	ND	+	ND	ND	
Acarian	Apple growers	[27]	4	NA	+	ND	Neg precipitins	ND	
Daphnia	Fish food-store	[28]	2	NA	+	+	ND	2/2 +	
Weeping fig	Plant keepers	[29]	84	7	21% +	21%	ND	100% of 6 +	PC_{20}
Sheep blowfly	Technicians	[30]	53	24	ND	67% of 15 +	ND	ND	
Silkworm	Silk workers	[31]	53	34%	ND	ND	ND	ND	
Plants									
Grain dust	Grain elevators	[32]	610	~40	9% +	ND	Neg precipitins	ND	Spirometry pre-post shift
		[33, 34]	502	47	~50% of 51 exposed +	ND	ND	ND	FEV_1, volumes
		[35]	22	NA	0% +	ND	Neg precipitins	27% +	50% PC_{20} +
Wheat, rye and soya flour	Bakers, millers	[36]	279	35	9% + (cereals)	ND	ND	ND	FEV_1, PC_{20}
		[37]	7	100	100%+	100%+	100% neg	57% +	
		[38]	9	100	ND	100% +	Western blotting, *etc.*	ND	
Lathyrus sativus	Flour handler	[39]	1	NA	+	ND	+ precipitins	+	
Vicia sativa	Farmer	[40]	1	NA	+	+	+ precipitins, passive transfer	+	
Buckwheat	Bakers	[41]	3	NA	100% +	ND	ND	ND	
Gluten	Bakers	[42]	1	NA	+	+	RAST inhibition	+	
Coffee bean	Food processor	[43]	372	34	24% +	12% +	ND	ND	Function tests
		[44]	45	9	9–40% +	ND	ND	ND	Spirometry
		[45]	22	NA	82% +	50% +	ND	67% of 12 +	PC_{20} + in 14
Castor bean	Oil industry	[46]	14	NA	100% +	100% +	ND	ND	
Tea	Tea processors	[47]	3	NA	100% neg	ND	ND	100% of 3+	
Herbal tea	Herbal tea processors	[48]	1	NA	ND	Neg	ND	+	

The number of subjects tested is not specified if it included all subjects; otherwise it is mentioned. [§]: Prevalence of symptoms compatible with work-related asthma unless otherwise stated. *: based on challenge data; **: presence of bronchial hyperresponsiveness; [†]: subjects with symptoms. All proportions including 3 or more as the denominator are expressed as %. BAL: bronchoalveolar lavage; 3-DMAPA: 3-(dimethylamino)-prophylamine; EPO: expoxy; FEV_1: forced expiratory volume in one second; HDI: hexamethylene diisocyanate; HSA: human serum albumin; IgG: immunoglobulin G; indust: industry; manuf: manufacturer; MDI: methylene diphenyldiisocyanate; NA: not applicable; ND: not done; neg: negative. PCA: passive cutaneous analphylaxis; PC_{20}: provocative concentration producing a 20% fall in FEV_1; PEFR: peak expiratory flow rate: PPI: polymethylene polyphenylisocyanate; RAST: radioallergosorbent test; TDI: toluene diisocyanate;

Table 1. continued

Agents	Occupation	[Ref]	Subjects n	Prevalence %	Skin test	Specific IgE	Other immunologic	Broncho-provocation test	Other evidence
Tobacco leaf	Tobacco manufacturers	[49]	1	NA	+	+	ND	+	
		[50]	16	69	ND	ND	ND	ND	PEFR monitoring
Hops	Brewery chemist	[51]	1	NA	+	ND	ND	ND	
Baby's breath	Florist	[52]	1	NA	+	+	Histamine release	+	
Freesia and paprika	Horticulture	[53]	2	NA	+	+	Histamine release	ND	
Mushroom	Mushroom soup processors	[54]	8	NA	+	ND	ND	50% of 8 +	
Cocoon seed	Decorator	[55]	1	NA	+	ND	ND	ND	
Chicory	Chicory grower	[56]	1	NA	Neg	ND	ND	ND	FEV_1, PC_{20}
Rose hips	Pharmaceutical	[57]	9	NA	67% +	67% +	ND	50% of 4 +	
Sunflower	Laboratory workers	[58]	1	NA	+	+	RAST inhibition	+	
Garlic dust	Food packaging	[59]	1	NA	+	+	ND	+	
		[60]	1	NA	+	+	RAST inhibition	+	
Lycopodium	Powder	[61]	30	7	ND	ND	ND	2/2 +	
Sericin	Hairdresser	[62]	2	NA	1/1+	ND	ND	ND	
Nacre dust	Nacre buttons	[63]	1	NA	+	ND	Neg precipitin	+	
Pectin	Christmas candy maker	[64]	1	NA	+	-	Specific IgG_4	+	
Henna (conchiolin?)	Hairdressers	[65]	2	NA	+	+	ND	1/2 +	
Neurospora	Plywood factory worker	[66]	1	NA	+	+	ND	+	
Biologic enzymes									
B. subtilis	Detergent industry	[67]	1642	3.2 (over 7 yrs)	4.5–75% +	26% of 248 +	ND	ND	Lung function
		[68]	38	NA	66% +	ND	Passive transfer 100% of 5 + precipitin (nonspecific)	90% +	Lung function
			667	NA	ND	5%	ND	ND	
Trypsin	Plastic, pharmaceutical	[69]	14	29	+	+	ND	75% of 4 +	
Papain	Pharmaceutical	[70]	29	45	34% +	34% +	ND	89% of 9 +	
Pepsin	Pharmaceutical	[71]	1	NA	+	+		+	
Pancreatin	Pharmaceutical	[72]	14	NA	93% +	100% of 3 +	ND	100% of 8 +	Lung function
Flaviastase	Pharmaceutical	[73]	3	NA	+	+	+ precipitin	ND	
Bromelin	Pharmaceutical	[74]	76	11	25% +	ND	ND	ND	
		[75]	2	NA	+	ND	ND	2/2+	
Egg lysosyme	Pharmaceutical	[76]	1	NA	+	+	ND	+	+ PEFR monitoring
Fungal amylase	Bakers	[77]	118	NA	100% of 10 +	2% exposed + 34% occup. asthma +	ND	ND	
		[78]	1	NA	+	+	ND	+	
Fungal amyloglucosidade and hemicellulase	Bakers	[79]	140	NA	ND	5–24%	ND	ND	
Esperase	Detergent industry	[80]	667	NA	ND	5%	ND	ND	
Vegetable gums									
Acacia	Printers	[81]	63	19% of 31 (selection)	ND	ND	ND	ND	
		[82]	10	NA	+	ND	passive transfer (3+)	ND	
Tragacanth	Gum importer	[83]	1	NA	+	ND	ND	ND	
Karaya	Hairdressers	[84]	9	4	+	ND	Passive transfer	ND	
Guar	Carpet manufacturing	[85]	162	2	5% +	8% +	ND	67% of 3 +	PC_{20}
Other									
Crab	Snow-crab processors	[86]	303	16	22% +	ND	ND	72% of 46 +	PEFR + PC_{20} monitoring
Prawn	Prawn processors	[87]	50	36	26% +	16% +	ND	2/2 +	
Hoya	Oyster farm	[88]	1413	29	82% of 511 with asthma +	89% of ~180 with asthma +	ND	ND	
Cuttle-fish	Deep-sea fishermen	[89]	66	Incidence of 1%/yr	ND	ND	ND	ND	
Trout (?)	Trout-processors	[90]	5	NA	ND	100% neg	100% +	ND	
Shrimp meal	Technician	[91]	1	NA	+	+	ND	+	
Larva of silkworm	Sericulture	[92]	5519	0.2	100% of 9 (?) +	1/1 (?) +	P-K reaction	100% of 9 +	
Egg protein	Egg producers	[93]	188	7	34% +	29% +	ND	ND	PEFR, 7% +
Fish-feed (Echinodorus larva)	Aquarium keeper	[94]	1	NA	+	+	ND	+	
Red soft coral	Fishermen	[95]	74	9	2/2 +	ND	ND	ND	

For abbreviations see beginning of table. References are placed at the end of the table.

Table 1. continued

Agents	Occupation	[Ref]	Subjects n	Prevalence %	Skin test	Specific IgE	Other immunologic	Broncho-provocation test	Other evidence
Low molecular weight agents									
Diisocyanates									
Toluene diisocyanate	Polyurethane	[96]	112	12.5	3% +	0% +	0% + PCA	45% of 11 +	
	Plastics, varnish	[97]	26		ND	19% +	ND	100% +	
		[98]	195	28.0	ND	5% +	ND	70% of 17 +	
		[99]	91			ND	0% + Specific IgG	ND	
		[100]	162†		ND	ND	ND	57% +	
Diphenylmethane diisocyanate	Foundry	[101]	11		ND	27% +	36% + Specific IgG	55% +	
		[102]	76	13.2	ND	3% +	7% + Specific IgG	ND	
		[103]	26	27.0	4% +	4% +	15% + specific IgG	ND	
1,5 naphthylene diisocyanate	Manuf. rubber	[104]	3		ND	ND	ND	100% +	
Isophorone diisocyanate	Spray painter	[105]	1		ND	ND	ND	+	
Prepolymers of TDI	Floor varnishers	[106]	2	NA	ND	0% +	Specific IgG-	+	
Prepolymers of HDI	Spray painters	[107]	9	45%	ND	33% +	56% +	+	
Combination of diisocyanates									
TDI, MDI, HDI, PPI	Paint shop	[108]	51	11.8*	ND	ND	ND	60% of 10 + to PPI	
TDI, MDI, HDI	Various indust.	[109]	24		ND	ND	ND	70% + to TDI 33% to MDI 33% of 9 + to HDI	
		[110]	247†		60% of 53 + 14%	ND	ND		
	Paint shop	[111]	62		ND	15% +	47% + specific IgG	6% to TDI 16% to MDI 24% to HDI	
TDI, MDI		[112]	28		ND TDI-HSA 83% of 6 + MDI-HSA	27% of 22 +	ND	100% +	
Anhydrides									
Phthalic anhydride	Plastics	[113]	1		+	+	ND	+	
	Tool setter, resin plant agent	[114]	3		ND	ND	ND	100% +	
	Production of resins	[115]	118	28	18% of 11 +	ND	ND		
		[116]	60	14	ND	7% +	7% + specific IgG	ND	
Trimellitic	Epoxy resins, plastics	[117]	4		100% +	75% +	100% + Specific IgG	100% of 1 +	
Tetrachlorophthalic anhydride	Epoxy resins, plastics	[118]	5		ND	ND	ND	100% +	
		[119]	7		100% +	100% +	ND	100% +	
Pyromellitic dianhydride	Epoxy adhesive	[120]	7		ND	ND	ND	30% +	
Methyl tetrahydrophthalic anhydride	Curing agent	[121]	1		+	+	specific IgG	ND	Improvement with removal
Hexahydrophthalic anhydride	Chemical worker	[122]	1	NA	ND	ND Evidence	ND Test	+	PEFR monitoring +
Himic anhydride	Manufacture of flame retardent	[123]	20	35	ND	40% of 7 +	RAST inhibition	ND	
Aliphatic amines									
Ethyleneamines									
Ethylene diamine	Shellac handlers	[124]	7		100% +	ND	ND	100% +	
	Photography	[125]	1		ND	ND	ND	+	
Hexamethylene tetramine	Lacquer handlers	[124]	7		100% +	ND	ND	100% +	
Triethylene tetramine	Aircraft fitter	[114]	1		ND	ND	ND	+	
Mixture of trimethyl-hexanediamine and isophorondiamine	Floor covering material salesman	[126]	1	NA	-	ND	ND	+	+ BAL
Ethanolamines									
Monoethanolamine	Beauty culture	[124]	10	100% +	ND	ND	100% +		
Aminoethyl-ethanolamine	Soldering	[127]	3		ND	ND	ND	100% +	
	Cable jointer	[128]	2		ND	ND	ND	+	
Dimethylethanolamine	Spray paint	[129]	1		-	ND	ND	+	

For abbreviations see beginning of table. References are placed at the end of the table.

Table 1. continued

Agents	Occupation	[Ref]	Subjects n	Prevalence %	Skin test	Specific IgE	Other immunologic	Broncho-provocation test	Other evidence
Other									
(3-DMAPA)	Ski manufacture	[130]	34	11.7	ND	ND	ND	ND	Cross-shift changes in FEV_1
Heterocyclic amines									
Piperazine	Chemist	[131]	2		50%	ND	ND	100%	
hydrochloride	Pharmaceutical	[132]	131	11.4	ND	ND	ND	100% of 1 +	
	Chemical plant	[133]	2		50% +	100% +	ND	ND	
N-methylmorpholine		[134]	48	16.6**	ND	ND	ND	ND	
Aromatic amines									
Paraphenylene diamine	Fur dyeing	[135]	80	37.0	66% +	ND	ND	74% +	
Mixture of amines									
EPO 60	Mould maker	[136]	1	NA	ND	ND	ND	+	
Fluxes									
Colophony	Electronic workers	[137]	34		ND	ND	ND	100% +	
	Manufacture solder flux	[138]	68 low	4	ND	ND	ND	ND	
			14 med	21	ND	ND	ND	ND	
			6 high	21	ND	ND	ND	ND	
Zinc chloride and ammonium chloride flux	Metal jointing	[139]	2		ND	ND	ND	+	Changes in PC_{20}
95% alkylarul polyether alcohol +5% polypropylene glycol	Electronic assembler	[140]	1		ND	ND	ND	+	
Wood dust or bark									
Western red cedar	Carpentry	[141]	35		ND	ND	ND	ND	Improvement on
(*Thuja plicata*)	Furniture making	[142]	1320	3.4	1.9% +	ND	ND	ND	removal
	Cabinet-making, carpentry	[143]	22		100% -	ND precipitin	100% -	82% +	
	Sawmill	[144]	185		100% -	ND	ND	100% +	
		[145]	652	4.1	100% -	ND	ND	ND	Questionnaire
California redwood (*Sequoia sempervirens*)	Woodcarvers	[146]	2		-	ND	- precipitin	+	
	Carpenter	[147]	1		ND	ND	ND	+	
Cedar of Lebanon (*Cedra libani*)		[148]	6		17% +	ND	100% - precipitin	ND	
Cocabolla (*Dalbergia retusa*)		[149]	3		100% -	ND	ND	ND	Improvement on removal
Iroko		[150]	1		+	ND	+ precipitin	+	
(*Chlorophora excelsa*)	Carpenter	[151]	1		ND	ND	ND	+	
Oak (*Quercus robur*)		[152]	1		-	ND	+ precipitin	+	
Mahogany (*Shoreal* Sp.)		[152]	1		-	ND	+ precipitin	+	
Abiruana (*Pouteria*)		[153]	2		+	ND	- precipitin	+	
African maple (*Triplochiton scleroxylon*)		[154]	2		+	+	Passive transfer	+	
Tanganyika aningre		[155]	3		100% +	100% -	100% - precipitin	100% +	
Central American walnut (*Juglans olanchana*)		[156]	1		-	-	- precipitin	+	
Kejaat (*Pterocarpus angolensis*)		[157]	1		+	ND	ND	ND	
African zebrawood (*Microberlinia*)		[158]	1		+	+	ND	+	
Ramin (*Gonystylus bancanus*)	Woodworker	[159]	2		+	+	ND	+	
Quillaja bark	Factory to produce Saponin	[160]	1		ND	+	ND	+	
Fernambouc (*Caesalpinia echinata*)	Bow-making	[161]	36	33.3	100% -	ND	ND	100% of 1 +	
Ashwood (*Fraxinus americana*)	Sawmill	[162]	1		-	-	ND	+	

For abbreviations see beginning of table. References are placed at the end of the table.

Table 1. continued

Agents	Occupation	[Ref]	Subjects n	Prevalence %	Skin test	Specific IgE	Other immunologic	Broncho-provocation test	Other evidence
Pau Marfim (*Balfourodendron riedelianum*)	Wood-worker	[163]	1	NA	+	+	ND	+	ND
Capreuva (*Myyrocarpus fastigiatus Fr. All.*)	Parquet floor layer	[164]	1	NA	ND	ND	ND	+	ND
Eastern white cedar (*Thuja occidentalis*)	Sawmill	[165]	1		ND	-	ND	+	PEFR recording
Ebony wood (*Diospyros crassiflora*)		[166]	1		-	ND	ND	+	
Kotibe wood (*Nesorgordonia papveifera*)		[167]	1		+	ND	Passive transfer	+	
Cinnamon (*Cinnamomum zeylanicum*)		[168]	40	22.5	ND	ND	ND	100% of 1+	
?	Sawmills of Eastern Canada and USA	[169]	11	ND	ND	ND	ND	+ PEFR monitoring	
Metals									
Platinum	Platinum refinery	[170]	16		62% +	ND	ND	62% +	
		[171]	136	29	17% +	21% +	ND	ND	
Nickel	Metal plating	[172]	1		+	ND	- precipitin	+	
		[173]	1		+	ND	- precipitin	+	
		[174]	1		+	+	ND	+	
Cobalt	Hard metal grinders	[175]	4		25% +	ND	ND	50% +	
	Diamond polisher	[176]	3		ND	ND	ND	100% +	
Zinc fumes	Solderers	[177]	2		ND	ND	ND	+	
	Locksmith	[178]	1		ND	ND	ND	+	
Tungsten carbide	Grinder	[179]	1		ND	ND	ND	ND	Recovery on removal
Chromium	Printer	[180]	1		+	ND	ND	ND	
	Plater	[181]	1		+	ND	ND	ND	
Chromium and nickel	Welder	[182]	5		ND	ND	ND	100% of 2 +	
	Tanning	[183]	1		-	+	ND	+	
Cobalt and nickel		[184]	8		75% + cobalt 62% + nickel	62% + cobalt 50% + nickel	ND ND	100% + to both cobalt and nickel	
Drugs									
Penicillins and ampicillin	Pharmaceutical	[185]	4		100% -	ND	ND	75% +	
Penicillamine	Pharmaceutical	[186]	1		ND	-	ND	+	PEFR recording
Cephalosporins	Pharmaceutical	[187]	2		+	ND	ND	+	
	Pharmaceutical	[188]	91	7.7	7.1% +	ND	ND	ND	Improvement off-work
Phenylglycine acid chloride	Pharmaceutical	[189]	24	29	37% +	37% +	Passive transfer	100% of 2 +	
Psyllium	Laxative manuf.	[190]	3		100% +	ND	ND	60% +	
	Pharmaceutical	[191]	130	4*	19% of 120 +	26% of 118 +	ND	27% of 18 +	
	Nurses	[192]	5		80% +	100% +	ND	100% +	
	Health personnel	[193]	193	4*	3% +	12% of 162 +	ND	26% of 15 +	
Methyl dopa	Pharmaceutical	[194]	1		-	ND	ND	+	
Spiramycin	Pharmaceutical	[195]	1		+	ND	ND	+	
	Pharmaceutical	[196]	51	7.8*	100% -	ND	ND	25% of 12 +	
	Pharmaceutical	[197]	2		ND	-	ND	+	
Salbutamol intermediate	Pharmaceutical	[198]	1		-	ND	ND	+	
Amprolium	Poultry feed mixer	[199]	1		ND	ND	ND	+	
Tetracycline	Pharmaceutical	[200]	1		ND	ND	ND	+	
	Pharmaceutical	[201]	1		+	ND	ND	+	
Isonicotinic acid hydrazide	Hospital pharmacy	[202]	1		+	+	ND	+	
Hydralazine	Pharmaceutical	[203]	1		-	-	- Specific IgG	+	
Tylosin tartrate	Pharmaceutical	[204]	1		ND	ND	ND	_	
Ipecacuanha	Pharmaceutical	[205]	42	47.6	52% of 19 +	66% of 18 +	ND	ND	
Cimetidine	Pharmaceutical	[206]	4		ND	ND	ND	25% +	
Opiate compounds	Pharmaceutical	[207]	39	26%	+	ND	ND	ND	PEFR pre-post shift FEV_1

For abbreviations beginning end of table. References are placed at the end of the table.

Table 1. continued

Agents	Occupation	[Ref]	Subjects n	Prevalence %	Skin test	Specific IgE	Other immunologic	Broncho-provocation test	Other evidence
Chemicals									
Chloramine T	Chemical manuf.	[208]	6		100% +	ND	66% + passive transfer	ND	
	Brewery	[209]	7		100% +	ND	ND	ND	Recovery with removal
	Janitor-cleaning	[210]	5		100% of 4 +	ND	ND	100% of 3 +	
Polyvinyl chloride	Meat wrapper	[211]	96	69.0	ND	ND	ND	27% of 11+	
(fumes)	Meat wrapper	[212]	3		ND	ND	ND	ND	History only
(powder)	Manuf. bottle caps	[213]	1		ND	ND	ND	+	PEFR recording
Ethylcyanoacrylate ester	Building airplane models	[214]	1		ND	ND	ND	+	
Organic phosphate insecticides	Chemical packaging plant	[215]	1		ND	ND	ND	ND	History only
Levafix brilliant yellow E36	Pre dye solution	[216]	1		+	ND	ND	+	
Drimaren brilliant Yellow K-3GL	Textile industry	[216]	1		+	ND	ND	+	
Cibachrome brilliant scarlet 32	Textile industry	[216]	1		+	ND	ND Evidence	+ Test	
Drimaren brilliant blue K-BL	Textile industry	[216]	1		+	ND	ND	+	
Reactive dyes	Reactive dyes manufacture	[217]	309	25.2 8% + black	7% + orange 17% + black	17% + orange	ND	65% of 20 +	
Lanasol yellow 4G	Dyer	[218]	1	NA	+	ND	ND	+	
Persulphate salts	Hairdressing	[219]	2		+	ND	ND	+	
& henna	Hairdressing	[220]	2		+	ND	ND	+	
	Hairdressing	[221]	23	17.4	4% +	ND	ND	100% of 4 +	
	Hairdressing	[222]	1		-	ND	ND	+	
	Hairdressing	[223]	1		ND	ND	ND	+	
Azodicarbonamide (azobisformamide)	Plastics, rubber	[224]	151	18.5	ND	ND	ND	ND	Removal with improvement
	Plastic	[225]	2		ND	ND	ND	+	
	Plastics	[226]	4		ND	ND	ND	100% of 2 +	
Diazonium salt	Manuf. of photocopy paper	[227]	1		ND	ND	ND	+	
	Manuf. of fluorine polymer precursor	[228]	45	55.5	ND	20% +	ND	100% of 2	
Hexachlorophene (sterilizing agent)	Hospital staff	[229]	1		ND	ND	ND	+	
Formaldehyde	Hospital staff	[230]	28	29*	ND	ND	ND	50% of 4 +	
	Different indust.	[231]	15		ND	ND	ND	60% +	
		[232]	230	5.2	ND	ND	ND	5% +	
Urea formaldehyde	Resin	[233]	2		-	ND	ND	+	
	Manuf. of foam	[234]	1		ND	ND	ND	+	
Freon	Refrigeration	[235]	1		ND	ND	ND	+	
Furfuryl alcohol (furan based resin)	Foundry mold making	[236]	1		ND	ND	ND	+	
	Wool dye house	[237]	6		ND	83% +	100% +	ND	
Styrene	Plastics factory	[238]	2		-	ND	ND	+	
Glutaraldehyde	Hospital endoscopy unit	[239]	9	88.8	ND	ND	ND	ND	Questionnaire
Methyl methacrylate and cyanocrylates	Adhesive	[240]	7		ND	ND	ND	86% +	PEFR 14% +
	Nurse	[241]	1		ND	ND	ND	+	
Iso-nonanyl oxybenzene sulphonate	Lab. technician	[242]	1		ND	ND	ND	+	
Chlorhexidine	Nurse	[243]	2		ND	ND	ND	+	
Tetrazene	Detonator manuf.	[244]	1		ND	ND	ND	+	+ PEFR recording
Ethylene dioxide	Nurse	[245]	1	NA	ND	+	ND	+	Changes in PC_{20}
Polyethylene	Paper packer	[246]	1	NA	ND	ND	ND	+	+ PEFR recording
Tetracholoro-isophthalonitrile (fungicide)	Farmer	[247]	1	NA	ND	-	+ patch test	+	FEV_1 recording at work
Tributyl tin oxide (fungicide)	Venipuncture technician	[248]	1	NA	-	ND	ND	+	
Tall oil (pine resin)	Rubber tyre manufacturer	[249]	1	NA	-	ND	-patch test	+	+ PEFR recording

Synthetic materials

See beginning of table. References are placed at the end of the table.

Table 1. continued

Agents	Occupation	[Ref]	Subjects n	Prevalence %	Skin test	Specific IgE	Other immunologic	Broncho-provocation test	Other evidence
Plexiglass		[250]	1		ND	ND	ND	+	
Latex	Glove manuf.	[251]	81	6	11% +	ND	ND	ND	PEFR recording. Pre-post shift change in FEV_1
Unidentified									
(?)	Resp. therapist	[252]	194	18.7	ND	ND	ND	ND	Questionnaire
(?)	Mineral analysis laboratory	[253]	21	23.8*	ND	ND	ND	ND	Questionnaire PC_{20}
(?) Oil mists	Toolsetter	[254]	1		ND	ND	ND	+	PEFR recording
(?) Fluorine	Potroom	[255]	52		ND	ND	ND	ND	History
(?) Aluminum	Potroom	[256]	227	7.0	ND	ND	ND	ND	Questionnaire
	Potroom	[257]	35		ND	ND	ND	ND	History
	Potroom	[258]	57		ND	ND	ND	ND	History

For abbreviations beginning end of table. References are placed at the end of the table.

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