Prevention of work-related airway allergies

Recommended occupational exposure limits and periodic screening

Gezondheidsraad **President**
Health Council of the Netherlands

To the Minister of Social Affairs and Employment

Subject : Presentation of advisory report *Prevention of work-related airway allergies. Recommended occupational exposure limits and periodic screening*
Your reference: ARBO/P&G/2005/24294
Our reference : 455/JR/648-Y1
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Dear Minister,

The most commonly reported airway illnesses arise from workplace exposure to allergens. This is a significant problem, because the acquired allergic hypersensitivity may become irreversible. This advisory report deals with the management of the risk on work-related airway allergies by means of recommended occupational exposure limits, which serve as a basis for setting up occupational exposure limits (OELs), and periodic screening. Regarding recommended OELs, the first step is to judge whether so-called health-based recommended OELs can be derived. If that is not possible, it should be evaluated whether so-called reference values can be derived. In the latter case, regulatory authorities should make a choice on the accepted level of risk on allergic hypersensitivity. Furthermore, periodic screening in the workplace is a potentially valuable tool to be considered, provided that workers are properly informed about the potential consequences of a positive test result.

A point of particular attention to the foregoing is, however, that at the moment only for a small number of allergens sufficient investigations are performed on the toxicity, to be able to establish recommended OELs. Also to be able to set up periodic screening more investigations are needed. Consequently, there is a need for stimulating research on other allergens. Also attention should be paid to developing reliable exposure methods and immunological tests. Furthermore, there is a need for information regarding the suitability of periodic screening. It is therefore of importance to keep an eye on other preventive measures, which are available to the government and the business community, to manage risks on adverse health effects in the workplace.

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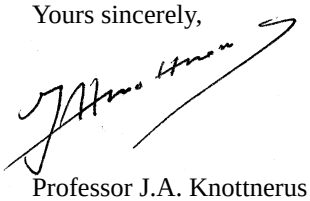
The advisory report is prepared by a specially convened committee of the Health Council. This committee has gratefully taken comments into account, which were received on a draft that was released for public review. It, furthermore, took advantage of consulting advice of two permanent boards of experts of the Health Council: the standing committees Health and Environment, and Infectious Diseases en Immunity.

A copy of this advisory report is also presented to the Minister of Health, Welfare and Sport, and to the Minister of Housing, Spatial Planning and the Environment.

Yours sincerely,



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Prevention of work-related airway allergies

Recommended occupational exposure limits and periodic screening

to:

the Minister of Social Affairs and Employment

No. 2008/03E, The Hague, March 13, 2008

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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Executive summary

Allergic respiratory disorders are a significant problem

Occupational allergic disorders are commonly reported illnesses arising from exposure to allergens. An allergic disorder is a significant problem because, if exposure continues, the symptoms may worsen and the acquired hypersensitivity may become irreversible. Hence, the consequences of allergen exposure can be far-reaching. Workers' health should therefore be protected by managing exposure to allergens.

One of the tools available for exposure management is the application of occupational exposure limits (OELs). An OEL is the maximum permissible occupational exposure level to a given airborne substance. OELs are applied by the government and the business community.

OELs are derived from 'toxicology-based recommended occupational exposure limits', which are based on scientific knowledge. One example of the latter type of exposure limit is a 'health-based recommended occupational exposure limit' for a non-carcinogenic substance. Such a limit specifies a level of exposure to an airborne substance, a threshold level, at or below which it may reasonably be expected that there is no risk of adverse health effects.

However, the validity of using the established procedures and methods to calculate health-based OELs for allergens has been questioned. Of particular significance in this regard is the question of whether it is possible to determine a threshold level. There are grounds for believing that any exposure, however

small, entails *some* risk of sensitisation and of developing allergic respiratory disorders if exposure continues.

At the request of the Minister of Social Affairs and Employment, a specially convened committee of the Health Council has sought to identify the best procedure and method for calculating recommended OELs for allergens which are inhaled in the workplace. In addition, the committee has considered whether the introduction of periodic screening would reduce the impact of these allergens on workers' health.

Without intervention, sensitisation leads to respiratory allergies

Allergy is a hypersensitivity reaction that is initiated by a specific immune response to a foreign agent, an allergen, at an exposure level that is normally tolerated. One of its characteristics is increased sensitivity of the immune system (sensitisation), induced by earlier exposure. Sensitisation may be asymptomatic, insofar as the sensitised individual experiences no physical symptoms. Several instances of exposure may be required before evidence of allergic sensitisation is seen. The risk on sensitisation differs among individuals; genetic predisposition plays a role in that.

In a sensitised person, renewed exposure may ultimately lead to allergic respiratory symptoms (*i.e.*, allergic rhinitis, rhinoconjunctivitis, and asthma). It has been observed that, if exposure continues after sensitisation, symptomatic conditions are liable to develop in several dozen percent of cases. The committee therefore makes the precautionary assumption that, in the event of continued exposure, almost all sensitised workers will ultimately develop allergic respiratory disorders.

Allergic respiratory disorders may lead to irreversible health problems

Allergic respiratory symptoms may be mild to begin with, but become more serious as exposure continues. The respiratory symptoms associated with allergy are not unique to allergy; definite diagnosis therefore requires immunological testing.

It is also possible for symptoms to become chronic, and not disappear when exposure is discontinued. For instance, it is estimated that about half of the workers who develop occupational allergic asthma still experience asthmatic symptoms years after exposure has ceased.

However, the sooner diagnosis is made after the appearance of symptoms, and the sooner exposure is ended, the better the prognosis is. The long-term

avoidance of exposure can even lead to the disappearance of detectable sensitisation. However, in most cases, once a person has been sensitised, he or she will remain hypersensitive for the rest of his or her life and liable to develop the same allergic respiratory symptoms in the event of renewed exposure to the relevant allergen. No curative treatment is currently available to reverse this hypersensitivity.

Respiratory allergy is a contributor to disease burden both at the personal level and at societal level. It also reduces quality of life, as reflected in physical, social and daily well-being, by affecting things such as career prospects, the presence of physical and mental problems, absenteeism and work disability.

Various agents can induce an allergy

There is a great variety of compounds, which cause allergic respiratory disorders in the workplace. They are divided into those with a high molecular weight and those with a low molecular weight.

The first group consists mainly of proteins, such as those found in (wheat) flour, and the urine of laboratory animals. Such allergens mainly induce a direct immune response by an IgE-mediated mechanism. The second group consists mainly of small compounds, such as acid anhydrides and isocyanates. Immune responses are provoked only when such allergens are bonded to proteins found in the body, such as serum albumin.

The different types of allergen differ in their ability to induce an immune response. It is not yet entirely clear what factors are responsible for the differences, but it is known that the physical and chemical characteristics and other intrinsic properties of the allergen play a role.

The circumstances of exposure also may vary enormously. For instance, workers are often exposed to mixtures of allergens. When working with wheat flour dust, for instance, or using gloves containing natural latex powder, a worker can be simultaneously exposed to dozens of different wheat flour dust or latex allergens, which are released into the air.

Other factors play a role as well

Exposure to an allergen is the key event in the development of an occupational respiratory allergy. However, various other factors may also influence the development of such an allergy. These include exposure conditions, exposure pattern and simultaneous exposure to other substances.

Furthermore, personal factors, such as genetic predisposition, lifestyle, infections, and the fact that exposure outside the workplace may have occurred earlier, can increase the risk for developing an allergy.

In practice, it is difficult to quantify the significance of these risk factors for the development of occupational respiratory allergies, simply because not enough is yet known.

Respiratory allergies are common in certain working populations

In certain industries, the risk for developing allergic respiratory symptoms due to occupational inhalation of allergens is relatively high. These include people working in the baking and flour-processing industries, laboratory animal care, and the bell pepper and flower greenhouse cultivation industry, as well as people who are exposed to industrial enzymes, soluble platinum salts, isocyanates or acid anhydrides at work. Epidemiological data from these types of industries suggest that the risk may amount to several dozen percentage points, depending on the type of allergen and other factors. Hence, a substantial proportion of workers who are exposed to airborne allergens at work develop specific sensitisation and allergic respiratory diseases.

Sensitisation is the best basis for the calculation of toxicology-based OELs

An occupational exposure limit is based on the most ‘critical’ adverse health effect associated with the relevant substance. The critical effect may be the effect that is first observed when exposure increases, or the effect that is most significant in the development of disease.

Where allergic respiratory disorders are concerned, the committee is of the opinion that allergic sensitisation should be regarded as the critical effect. Allergic sensitisation is the best starting point for the calculation of OELs, since it plays a crucial biological role and is a prerequisite for the development of allergy. Once sensitisation has occurred, continued exposure will lead to allergy in most cases.

An exposure level below which no sensitisation develops can exist

Current scientific knowledge regarding the relevant allergic immunological mechanisms leads the committee to believe that it is plausible that a threshold level exists, below which no allergic sensitisation may be expected. This level

may be very low: so low, in fact, that little of an allergen is needed to provoke an allergic immune response.

Where a few allergens were concerned, the committee considered whether threshold levels could be deduced from the available epidemiological data. This does appear to be possible where soluble platinum salts are concerned. However, no evidence of a threshold level was observed for (wheat) flour dust, even at low levels of exposure. More detailed study is needed before conclusions may be drawn regarding other allergens.

Furthermore, the results of animal studies provide a mixed picture. For instance, a threshold level was observed in a few experiments, but in others not. The committee emphasises, however, that the outcomes of the animal experiments need to be interpreted cautiously, since the experimental exposure conditions tend to differ considerably from workplace exposure conditions. The design of the animal inhalation models could be improved as well.

Preferably health-based occupational exposure limit should be derived

Current knowledge suggests that a threshold level does exist for inhaled allergens. This implies that health-based recommended occupational exposure limits can be calculated for allergens using the same procedures and methods as those used for other non-carcinogenic substances. Hence, the first step towards calculating such a limit is to determine whether, in the given instance, it is possible to use a method such as the common no-observed-adverse-effect-level method, the benchmark dose method, or another similar statistical model for human data.

However, the committee believes that, where most allergens are concerned, it will not be possible to calculate a reliable health-based recommended occupational exposure limit by any such method. The reason being that, in most cases, the threshold level will be too low to discern using the techniques presently available.

If that is not possible, a reference value can serve as an alternative

The committee therefore proposes an alternative approach for those allergens for which no reliable health-based recommended OEL can be calculated by the established methods. This approach involves determining reference values, *i.e.* concentration levels that correspond to predefined accepted levels of risk of allergic sensitisation.

These reference values can then be used as a basis for assessing occupational exposure limits. The committee recommends that the predefined accepted level

of risk should take account of the background prevalence of the allergen in question. However, the final decision on the predefined accepted level of risk will also depend on policy and social considerations.

Periodic screening for allergic sensitisation can be an useful additional tool

Although occupational exposure limits are useful as a means of protecting workers' health, it should be taken into account that cases of allergic sensitisation and respiratory disorder can happen. One additional option available to the government and the business community is the early detection of sensitised workers, by means of periodic screening, for example.

In view of the prognosis associated with continued exposure and the high prevalence of allergic respiratory disorders in some occupational groups, the committee considers periodic screening for allergic sensitisation to be a potentially valuable tool – provided that workers are properly informed about the potential consequences of a positive test result. The latter proviso is important because, in the most extreme cases, the detection of sensitisation could have very far-reaching consequences for a worker.

The feasibility of periodic screening should be considered on a case-by-case basis

The committee, however, makes some comments on the feasibility of periodic screening in the workplace. For instance, periodic screening is of value only where accurate and reliable tests are available for the detection of allergic sensitisation to the relevant allergen. Such tests are available for certain well-known allergens, such as those found in flour dust, the urine of laboratory animals and in latex. Where other allergens are concerned, however, such tests still need to be developed. The allergens in question include those that can cause sensitisation by triggering a non-IgE-mediated immune response. As long as these immunological tests are not available, screening may focus on the detection of early symptoms and signs caused by allergy.

Another criterion is that periodic screening is performed at an acceptable price. In view of the number of cases of allergic respiratory symptoms in certain occupational groups, the committee assumes that screening is likely to be cost-effective for such groups. However, there is insufficient evidence to confirm that this is indeed the case, because no thorough cost-effectiveness studies have yet been performed.

In conclusion, the committee judges that it is worth to consider the introduction of periodic screening in addition to other tools available in managing exposure. Basically, periodic screening could be fairly and straightforwardly incorporated into the already existing, and statutory regulated periodic occupational health examination. The feasibility of periodic screening on allergic sensitisation, and what else is needed to comply with the most important criteria, should however be judged case-by-case.

Research requirements

At the moment, only for a small number of allergens sufficient toxicity and effectiveness studies are performed. For this reason it is important to stimulate research on other allergens. Also the development of reliable methods to measure exposure and of immunological tests demands attention. Furthermore, there is a need for information on the suitability of periodic screening.

Chapter 1

Introduction

1.1 Background to the ministerial request for advice

Allergic disorders have attracted increasing interest in recent years, not only from the general public, but also from occupational health professionals who help employers to protect their workers. Indeed, it is apparent that the most commonly reported occupational airway illnesses arise from workplace exposure to allergens.[180] Furthermore, for the individuals concerned, the implications of contracting such an illness can be far reaching. Therefore, the health of workers who are exposed to such substances in the workplace needs to be protected.

One of the tools available for that purpose is the occupational exposure limit (OEL). An OEL specifies the maximum permissible concentration of a given airborne substance, applied by the government and the business community to assess the significance of exposure in the workplace.

OELs are derived from toxicology-based recommended occupational exposure limits, which are calculated on the basis of scientific knowledge regarding the toxicity of the substance in question.[84] Where a non-carcinogenic substance is concerned, a so-called 'health-based recommended occupational exposure limit' is calculated from the available data. Such a limit is a specification of the level of substance, at or below which it may reasonably be expected that there is no risk of adverse health effects. In principle, allergens are among the substances that can be addressed on this basis.

Recommended occupational exposure limits are calculated in accordance with a procedure, and using methods, that are in widespread use and whose validity is widely acknowledged.[84-86] However, the methods for allergens has been questioned. The reason being that the Dutch Expert Committee on Occupational Standards (DECOS) concluded a while ago that no health-based recommended OEL could be calculated for wheat and other cereal flour dusts because, even at the lowest observed exposures, specific sensitisation effects were discernible.[104] Wheat flour dust is a known allergen, which causes allergic hypersensitivity and respiratory disorders among bakers and people working in bakeries and flour mills.

At about the same time, the Institute for Risk Assessment Sciences (IRAS) at the University of Utrecht and the Netherlands Organisation for Applied Scientific Research (TNO) reported to the Ministry of Social Affairs and Employment that no threshold level could be calculated for alpha-amylase, an enzyme that, like wheat flour dust, can trigger hypersensitivity and allergic respiratory disorders. For this enzyme too, no exposure level could be determined, below which the relevant effects did not occur.

It is believed that these observations are attributable, at least in part, to the allergens' effect mechanisms and allergenic properties. If this is the case, the two allergens referred to should not be viewed in isolation, and it is reasonable to suppose that the calculation of health-based OELs for other allergens could be problematic as well.

This situation was a matter of concern to the Minister for Social Affairs and Employment, because it could mean that the application of exposure limits is insufficient as a means of managing the health risks associated with occupational exposure to allergens. The Minister accordingly sought the advice of the Health Council.

1.2 Issues addressed

In April 2005, the Council received a letter, in which the Minister requested advice on a system for setting limits on occupational exposure to allergens, and on the possible introduction of periodic screening. The full text of the request is reproduced in annex A. This report focuses primarily on the following two questions:

- What is the best way of calculating exposure limits for inhaled allergens and thus of managing the risk of allergic disorders in workers who experience occupational exposure?

- If the occupational inhalation of allergens, regardless of the level of exposure, entails a risk of sensitisation or allergy development, would periodic screening for the illness or its precursors be a desirable and effective means of preventing aggravation?

This advisory report also addresses certain subordinate matters, such as immunological effect mechanisms; the seriousness of and prognosis associated with allergic respiratory disorders; the critical effect on which standards should be based; the prevalence of allergic sensitisation and respiratory disorders in the occupational population; risk factors and the relationship between exposure and response.

In section 10.3, at the end of this advisory report, the specific questions posed by the minister are answered individually.

1.3 The committee and its methodology

With a view to answering the State Secretary's questions, the President of the Health Council established a committee that was particularly assigned to take this advisory report in hand. The committee was installed on March 2006. The members of the committee are listed in annex B to this report.

At the start of the report preparation process, the Health Council looked at ways of coordinating the new committee's work with that of other Health Council committees working in related fields. At the time of the State Secretary's request, for example, the Committee on Food Allergies was preparing a report on allergic responses to food, in particular IgE-mediated food allergies, on behalf of the Minister of Health, Welfare and Sport and the Minister of Agriculture, Nature Management and Food Quality. In addition, the Committee on Asthma and Environmental Factors was looking into the influence of environmental factors on the development of asthma and respiratory allergies, at the request of the Minister of Housing, Spatial Planning and the Environment. Both advisory reports are published in 2007.[88,90]

In the summer of 2007, the president of the Health Council released a draft of the advisory report for public review. The individuals and organisations that commented on the draft are listed in annex C. The committee has taken these comments into account in deciding on the final version of the report.

1.4 Demarcation

This advisory report is confined to the subject of occupational exposure limits; it does not give consideration to any other regulatory instruments. Occupational exposure limits for compounds are namely one of the instruments of the government's health and safety at work policy. The aims of this policy are to define the risks associated with occupational exposure and to regulate such exposure by the definition of legally binding guidelines and methodologies. Its focuses are determining the permissibility of exposure, deciding on the measures that should be taken and enforcing the implementation of those measures.[83] Alongside the OEL testing regime, there is for instance also a legal requirement that general precautions should be taken to prevent or minimise the exposure experienced by people working with relevant substances. This requirement is in addition to the obligation that the employer has to draw up a risk assessment report, in which all possible risks to the safety, health and welfare of workers are identified and analysed. The guidelines are defined and tested by both the government and the business community.

Furthermore, this report deals exclusively with allergens that can affect the health of the working population by means of inhalation, since standardisation is intended to facilitate the regulation of airborne exposure only. Occupational exposure to allergens by direct skin contact is therefore outside the scope of this report. Dermal exposure is considered in this report only as a risk factor for the development of allergic respiratory disorders.

The committee's advice is based on scientific information and views, as published in generally available scientific literature, and as selected in order to produce a balanced report.

1.5 Structure of this report

The report begins with a review of current scientific knowledge in this field. Thus, chapter 2 explains what sensitisation and respiratory allergy are, what the symptoms are, how the illness progresses and what diagnostic techniques are used. Chapter 3 defines what allergens – and inhalant allergens in particular – are, which workplace agents can induce respiratory allergy, and how the presence of such agents in the air can be measured. Chapter 4 is devoted to the various risk factors that can influence the development of work-related allergic airway disorders. Estimates are presented in chapter 5 of the rates of allergic sensitisation and airway disorders among exposed workers. In chapter 6, the point of departure for

a recommended OEL is considered, and in chapter 7, the existence of a threshold level comes up for discussion. This lays the foundation of answering the question what the best way is of setting standards for allergens in chapter 8. Chapter 9 contains the committee's recommendations regarding periodic screening. Finally, in chapter 10, an outline is given of the most important conclusions. Also in that chapter, the separate questions made by the minister are answered point by point, and recommendations are given for research.

Chapter 2

Allergic respiratory disorders

What exactly is an allergy? How does such a condition develop and what different kinds of allergy are there? Furthermore, how does one distinguish an airway allergy and ascertain whether it is caused by occupational exposure? Finally, how does the illness progress? These questions are addressed in this chapter.

2.1 Definition

Allergy is defined by the European Academy of Allergology and Clinical Immunology (EAACI) and the World Allergy Organisation (WAO) as a hypersensitive response, triggered by an immunological mechanism.[82,128,129] Hypersensitivity causes objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose that is tolerated by normal subjects.

2.2 The development of allergy

Allergy is an illness of the immune system. Its basis is the generation of a specific immune response to a foreign agent – an allergen – leading to unwanted allergic inflammation.

There are two phases in the development of an allergy: the sensitisation or induction phase and the elicitation phase.[122,124] In the sensitisation phase, the immune system first comes into contact with the allergen and an immune response follows. Once this has happened, the immune system is in a state of

heightened readiness (sensitisation). Renewed exposure can then provoke an exaggerated immune response, possibly resulting in inflammation. Such inflammation may be accompanied by clinically discernible allergic symptoms (elicitation).

In other words, an allergy involves the immune system responding unnecessarily. The body has various regulatory mechanisms, which should prevent unnecessary activation of the immune system. However, scientific knowledge of the mechanisms in question and how they work remains sketchy. Various teams around the world are presently researching this field. What is known is that, in some people, these regulatory mechanisms do not work quite as they should, making the individuals in question vulnerable to sensitisation and to the development of allergic diseases. With that both hereditary and environmental factors play a role. However, it is presently not well possible to predict with confidence who is likely to develop an allergy and who is not.

2.3 Immune responses

Allergens can trigger various specific types of humoral or cellular immune responses. The dominant type of immune response associated with an allergy depends on the allergen involved (see chapter 3) and on the circumstances of exposure.

On the basis of the response type, the EAACI and WAO have proposed the categorisation of allergies as IgE-mediated allergies or non-IgE-mediated allergies (see Figure 2.1).[82,128,129] The main reason for distinguishing between these two groups is that the most extensively studied and discussed allergies primarily involve a humoral immune response, in which IgE antibodies play a key role.

The specific immune responses are highly complex, and do consist of a cascade of immunological processes, which involve various types of immune cells. First, allergens are caught by so-called antigen-presenting cells, which reside in the mucous membranes of the respiratory tract and are extremely mobile. Parts of these allergens subsequently find their way onto the surface of these cells and are then presented to specialised white blood cells, known as (naive) T_H0-helper cells.[124] These naïve T-cells are activated by contact with the antigen-presenting cells, in combination with other factors, causing them to differentiate to so–called T_H1-, T_H2-, T_H17-, and T-regulatory cells. These T-cell subsets control each other by positive and negative feedback mechanisms. It is suggested that it is the imbalance between the activation and suppression of these T-cells, and maybe other yet unknown T-cells, at the onset and during the course of allergy development, that determines ultimately whether an allergy develops.[1,74,127,239]

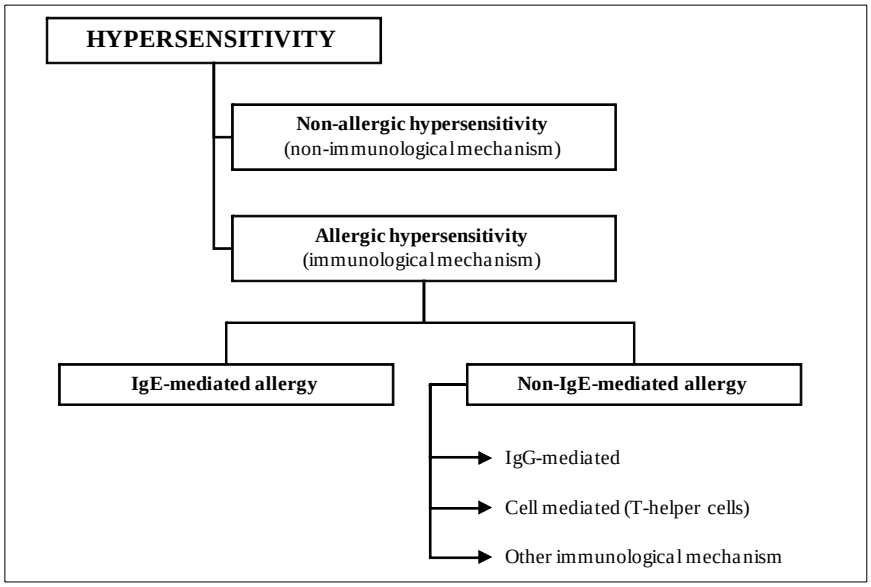

Figure 2.1 Forms of hypersensitivity, categorised on the basis of associated mechanism.[129]

Regarding IgE-mediated immune responses, the T_H2 cells play a central role. T_H2 cells produce cytokines (interleukines) that inhibit the activity of T_H1 cells, and stimulate B cells to mature into plasma cells.[62,230] The latter happens only along with the presence of (parts of) the allergen in question. The plasma cells then produce antibodies, immunoglobulins (Ig), which are able to recognise parts of the relevant allergen. Plasma cells are able to produce five kinds of immunoglobulins, including IgE. Each immunoglobulin E is able to recognise only one particular kind of allergen; in principle, therefore, there are as many IgE-immunoglobulins as allergens.

IgE-immunoglobulins activate other immune cells, the so-called mast cells, present locally in the mucous membranes of the respiratory tract. In response to initial exposure, the IgE immunoglobulins attach themselves to the surfaces of the mast cells, thus making them sensitive. When an IgE attached to a mast cell detects and secures (parts of) the allergen with which it is matched – typically in the event of renewed exposure – the mast cell is triggered to produce various chemical substances, which in turn cause inflammation.[24,124,162] This is known as the elicitation phase.

The consequences of this may be immediately apparent to the person involved, or may become so only some hours later, *i.e.* a considerable time after

the start of exposure.[124,171,183] The inflammation is characterised by: increased blood flow through and vascular dilation in the mucous membranes; increased mucous production; and, adaptation of the smooth muscle cells of the respiratory tract. The associated physical conditions include a running nose, nasal congestion resulting from swollen mucous membranes, irritation and redness of the eyes, sneezing, a phlegmy cough and/or shortness of breath.

IgE-mediated immune responses are also known as responses of the immediate type (type I reaction).

Non IgE-mediated allergies can be caused by different immune responses, of which the balance between de various T cell subsets play a role, and maybe other mechanisms as well.[124] An example is the IgG-mediated or cytotoxic immune response (type II reaction). This immune response breaks down cells and tissues, because of attacks of antibodies at the cell surfaces to which (parts of) allergens are bound. Regarding inhalation of allergens, to which this advisory report is focused, this type of allergy does not occur. Allergy also can be caused by the formation of so-called immune complexes (antigen-IgG complexes) in blood or tissues (type III reaction). Lastly, the immune response may be of the delayed type (type IV reaction). The delayed type of allergy is characterised by the presence of T_H1 cells and macrophages, which are stimulated to produce chemokines and cytokines by binding to (parts of) allergen, without intervention of antibody producing cells. This form of allergy is described for contact allergy to metals, such as nickel and chromium. All these immune responses may lead to local inflammation, and therefore may give physical symptoms. Based on these physical symptoms, however, it is not well possible to distinguish the immune response which is responsible for the symptoms. In any case, it is typical that the onset of non-IgE-mediated responses usually manifest not until hours after the start of exposure.[164]

It is worth noting that airway inflammation is not always caused by a specific immune response, but may also be the result of a non-specific response, such as irritation.[46,65,161] The associated ailments are comparable, and distinction is possible only by considering the overall pattern and investigating the cause.[168,250,265] Sometimes, allergic inflammation is caused by a combination of immune and non-immune responses by one and the same agent.

2.4 Exposure route

In the workplace, inhalation and skin contact are the two main exposure routes. Direct skin contact can induce phenomena such as eczema (redness, pruritus, flaking) and urticaria (redness, swelling). No further consideration is given to

this exposure route in this report, because it is concerned primarily with allergic airway diseases resulting from the inhalation of allergens.

The most common disorders associated with this exposure route are allergic rhinitis, and allergic asthma (bronchial).[82,128,129] Allergic rhinitis involves a hypersensitive or allergic inflammatory response by the nasal mucous membranes. In some cases, this is accompanied by inflammation of the connective tissues of the eye (rhinoconjunctivitis). Allergic asthma (bronchial) is a specific chronic inflammation of the respiratory tract resulting in shortness of breath. Allergic asthma should be discerned from irritant-induced asthma and reactive airway dysfunction syndrome, which are not caused by specific immune responses.[55,186]

Other allergic diseases in the airways include extrinsic allergic alveolitis, allergic laryngitis, and allergic eosinophilic bronchitis.[73,163,208] The former is an inflammatory response in the alveoli resulting from exposure to certain allergens.[94,141,208] An example of this condition is the farmers' lung, which initially involves influenza-like symptoms, but can culminate in pulmonary fibrosis in the event of chronic exposure. Allergic laryngitis entails inflammation of the larynx.[234] It is not yet known exactly which allergic immune responses are responsible for either condition, or how common either is in the working population. For these reasons, no further consideration is given to these disorders in the present context.

Normally, allergies associated with the inhalation of allergens involve only disorders of the respiratory tract. Sometimes, however, a general physical response can occur. Such a response – known as systemic anaphylaxis – is serious and potentially life threatening. However, the risk of anaphylaxis resulting from inhalation of allergens is very small.

2.5 Allergen sources

This report is concerned with allergens originating in the workplace, since the committee's remit was to consider work-related allergies. Examples of sources of allergens, which are well known to cause allergies outside the workplace environment, are food, medicines, and insect venoms. Allergies are sometimes also named to the allergen that is responsible for the allergy, such as house dust mite allergy, pollen allergy and cat allergy.

2.6 Diagnostics

Several steps are involved in determining whether a person has a work-related respiratory allergy.[95,168] First, the physician performs a general anamnesis, physi-

cal and function examinations, to establish whether the patient has an airway disease. If such a condition is diagnosed, the physician makes an occupational anamnesis with a view to determining whether the condition is the result of exposure to allergens at work. The final step is to try and identify the precise cause of the illness.

2.6.1 *Anamnesis and physical examination*

Physicians make use of diagnostic guidelines in order to determine the presence of particular disorders and to establish their general causes. Such guidelines indicate the questions that should be put to the patient and the nature of the physical examination that should be performed.[182,280]

The main characteristics of asthma are shortness of breath and a respiratory 'whistle', combined with cough or phlegm production. In addition, the patient is liable to experience diminished lung function and increased bronchial hyperresponsiveness in response to various non-specific stimuli (smoke, dust, cold). Allergic asthma is often accompanied by symptoms indicative of rhinitis of rhinoconjunctivitis.[44,64,207]

Rhinitis is characterised by sneezing, a running nose, nasal and/or ocular pruritus, nasal congestion and/or watery rhinorrhoea.[34,123,123,182] These symptoms are sometimes accompanied by sinusitis, which in turn causes headache. Rhinitis often occurs in combination with conjunctivitis (rhinoconjunctivitis).[238] In this condition, the nasal symptoms described above are accompanied by watering, burning, reddening and/or swelling of the eyes, and possibly by pruritus.[254] Distinction is made between intermittent and persistent rhinitis, on the basis of the nature and the duration of the symptoms.

2.6.2 *Occupational anamnesis*

The purpose of the occupational anamnesis is to establish whether there is a link between the illness and the patient's work. An occupational anamnesis is essential in order to arrive at a diagnosis of 'occupational respiratory allergy'. The focus of the investigation is the symptom development and exposure to potential allergens.[183] In most cases it concerns allergy that develops for the first time, but that is not always the case.[23,250]

2.6.3 *Clinical diagnostics*

A precise diagnosis in establishing occupational allergies requires specific immunological testing: performing tests on the patient to establish a positive link between his or her allergic condition and exposure to a particular allergen suspected of responsibility. The most widely used form of testing is skin prick testing, but serological testing is sometimes used as well. If the results of such tests are inconclusive, provocation testing by inhalation may be considered.

The three types of tests differ from one another in terms of what exactly they seek to establish. Furthermore, the findings of the tests are of diagnostic significance only in combination with anamnesis. Each type of test is considered in more detail below, and a number of observations are made regarding interpretation of the test results.

Skin prick test and serological testing

The purpose of a skin prick test (SPT) is to establish the presence of IgE-mediated hypersensitivity. This test is the first basic procedure for the diagnosis of an allergic condition. SPTs are suitable in the context of suspected food or inhalation allergies. The procedure involves applying a drop of allergen extract to the skin, then piercing the skin with a lancet, through the extract drop. After fifteen minutes, the diameter of any resulting swelling is measured, and the degree of reddening (erythema) around the prick site is observed. A swelling (wheal) with a diameter of 3 millimetres or more is generally regarded as a positive result.

Serological testing is a form of *in vitro* testing, whose object is to establish the total or specific IgE levels in a patient's blood. Most routine tests are based on either the RAST (Radio Allergo Sorbent Test) or the ELISA (Enzyme-Linked Immuno Sorbent Assay). The process involves linking allergen extracts to a carrier, to which serum from the blood of the subject is added. The allergen extracts may be obtained from a mixture of allergens, or from one particular allergen. Results are expressed in terms of kU/L (units per litre plasma), and sometimes in classes.[79,171] In recent years, total IgE level testing has lost significance, because, although a raised IgE level may indicate sensitisation to an allergen, it is known that a person with a normal IgE level may experience a strong positive response to a particular allergen.

It should be noted that both skin prick testing and serological testing are useful principally for establishing hypersensitivity to high molecular weight aller-

gens, such as proteins of plant or animal origin. With a handful of exceptions, they are less useful in relation to low molecular weight allergens.[168]

Furthermore, the tests are not always totally reliable. Reliability can be compromised by the variable quality of allergen extracts and the lack of standardisation.[23,204,235] (Pure) allergen extracts are commercially available, which have a stable composition and predetermined protein concentrations. However, these commercial extracts are mainly of everyday allergens, such as dust mites, pollen, fungi and domestic animal skin flakes.[128,129,183] By contrast, extracts of specific workplace allergens are provided by the plant. Since conditions often vary from one workplace to another and according to the activities being performed, and furthermore the preparation of extracts is not standardised, they are liable to differ greatly in their composition and purity, and therefore in their allergenic potency.

Finally, it should be recognised that test results can be influenced by factors such as reduced skin reactivity and the use of anti-inflammatory medication.[79] Furthermore, cross-reactivity – which involves the immune system mistaking one potential allergen for another – is possible.

Other immunological tests

There are immunological tests, which are based on other types of immune responses, and which do not depend on IgE-production. Two examples are lymphocyte or full blood proliferation tests and cytokine profiling.[62] These tests are still in development, and, therefore, it is too early to judge whether these can be used for screening purposes in the near future. Therefore, the committee abstains from going into more detail concerning the performance of these tests.

Specific inhalation provocation testing

Finally, there is a test to establish whether an allergen provokes a physical response (rhinitis, asthma), namely the nasal or bronchial provocation test. The test procedure involves a low dose of a known allergen being inhaled by the patient or introduced via the nose. Testing can take place in a specialist clinic or in the workplace, in which case a good clinical setting and an experienced tester are important, because there is a risk of the patient suffering a serious asthmatic attack. Provocation testing is not presently standardised. However, there are some common rules how to perform such testing.

In the scientific literature specific inhalation provocation testing are regarded as the gold standard for the diagnosis of work-related allergic asthma, if there is

little known about the exposure that may be causing the disease. However, such testing is not always reliable.[23,196] If, for example, the subject is exposed to an allergen other than that to which he or she is actually allergic, the result will be negative, even though the subject does have an allergy.[23,259] Furthermore, the subject's response may be attenuated if there has been no recent occupational exposure. On the other hand, a person with, for instance, unstable asthma may respond violently due to heightened sensitivity to non-specific stimuli.[23,259] Under such circumstances, the observed response may not be an allergic response to the particular allergen used for the test.

2.7 Course of the illness

A sensitised individual does not necessarily exhibit symptoms indicative of allergy. Such symptoms may develop, however, in response to continued exposure. It has been observed that, if exposure continues after sensitisation, symptomatic conditions are liable to develop in several dozen percent of cases (see Table 2.1). It is quite possible that the percentages given in the table would have been higher if the observation periods in the studies had been longer. The committee therefore makes the precautionary assumption that, in the event of continued exposure, almost all sensitised workers will ultimately develop allergic respiratory disorders.

Once a person has acquired an allergic respiratory condition, continued exposure is liable to aggravate it (make a mild condition serious) with the result that the condition ultimately becomes chronic.[201] People who initially 'merely' have symptoms of allergic rhinitis of rhinoconjunctivitis may develop asthmatic symptoms if exposure continues, particular if the allergen concerned is an allergen with a high molecular weight, but also such data were presented for allergens with a low molecular weight.[168,178,201,206] In a study by Malo *et al.* (1997), fourteen of twenty-four subjects who developed asthmatic symptoms had previously suffered from rhinitis, apparently attributable to exposure to protein-like allergens.[165] Of the twenty-four asthmatic subjects exposed only to non-protein-like allergens, only three had previously exhibited symptoms of rhinitis. This research team also reported that the interval between the development of rhinoconjunctivitis and the development of asthma averaged twenty-two months (with a wide range: from one month to eight years).

Table 2.1. Data on newly exposed symptom-free workers, who become sensitised due to exposure, and subsequently develop allergic airway symptoms.

Study duration and population	Number of participants	Number of symp/sens[a]	Percentage	Reference
Study duration: maximal 2 years				
• Apprentices of experimental animal facilities	38	6/7	90%	[228]
• Apprentices of experimental animal facilities and bakeries	118	7/11	64%	[60]
• Bakery apprentices	287	6/36-13/36[b]	16%-37%[b]	[267]
Study duration: maximal 4 years				
• Apprentices of experimental animal facilities	417	27/99 - 11/22[b]	27%-50%[b]	[76,78]
• Bakery apprentices	230	2/8-0/8[b]	25%-0%[b]	[75]
• Apprentices oral hygiene	122	2/7-1/7[b]	29%-14%[b]	[75]
• Exposure to industrial enzymes	1 207	78/324	24%	[149]
Study duration: maximal 5 years				
• Exposure to platinum salts	115	9/14	64%	[174]
Study of more than 5 years				
• Exposure to acid anhydrides (till 19 year)	401	10/12	83%	[20]

[a] symp/sens, persons with symptoms/sensitised persons.
[b] Nose and eye symptoms, and breathing problems, respectively.

Karjalainen *et al*. (2003) reported a follow-up study, which sought to quantify the increased relative risk of asthma for a person who initially suffers from work-related rhinitis.[134] The likelihood of developing asthma was greatest in the first year following rhinitis diagnosis. Analysis on the basis of allergen type found that people with allergic rhinitis and exposed to protein-like allergens (those who worked with animals, flour and in environments where storage mites were present) were at greater risk of developing asthma than people with allergic rhinitis exposed to non-protein-like allergens (acid anhydrides).

Where asthma is concerned, continued exposure may result in a faster diminution of lung function, the induction or aggravation of bronchial hyperresponsiveness and permanent changes to the respiratory tract.[108,186] In a handful of reported cases, occupational asthma has ultimately proved fatal.[108,168,186]

In most cases, allergic symptoms disappear or diminish when exposure is stopped, but reports are published that allergic disorders can persist even after exposure has entirely ceased.[5,19,47,49,97,108,146,168,186,198,201,202,202,214,215,265] For instance, it is estimated that roughly 50 to 70 per cent of patients with occupational asthma continue to experience symptoms and non-specific bronchial hyperresponsiveness years after the cessation of exposure.[186,200,265] Padoan *et al*. (2003) demonstrated that more than ten years after the cessation of occupational exposure to

the allergen toluene diisocyanate, 60 per cent of subjects still experienced symptoms of asthma and increased bronchial hyperresponsiveness to methacholine.[200] Whether a person recovers (partly or fully) depends on various factors, including the duration and intensity of exposure, the interval before diagnosis, the seriousness of the diagnosis, the type of allergen, the degree of respiratory hyperreactivity to non-specific substances (methacholine) and certain characteristics of the person in question (base-line lung function, genetic predisposition).[5,19,47,108,168,186,198,202,215,265] However, it is not known how each of these factors affect recovery. What is clear is that the earlier diagnosis is made and more conscientiously exposure is subsequently avoided, the better the prognosis.[146,188,215]

Chapter 3

How allergens work

Tens of thousands of agents are used in the various sectors of industry. It is pertinent to ask which of these agents can cause allergy in the event of inhalation, and what their characteristics are. These matters are discussed in this chapter.

3.1 Definition

An agent that can provoke an undesirable and specific immune response is referred to as an allergen.[82,128] An allergen that, when inhaled, is liable to cause an allergic respiratory disease is referred to in this report as an inhalant allergen. It is characteristic of allergens that not everyone who is exposed to them develops an allergic immune response.

Two related terms should also be defined: immunogen and antigen. An immunogen is an agent that is capable of provoking an immune response; an antigen is an agent that is the target of an immune response following recognition by the immune system. The term ‘allergen’ is reserved for those immunogenic and antigenic agents that trigger an *undesirable* specific immune response. In this report, the term ‘allergen’ is consistently used.

3.2 Types of allergens

A wide variety of workplace agents can cause allergic diseases. Many of the agents concerned are of biological origin, such as proteins. Such agents are gen-

erally common in the environment, but are nevertheless typical of particular occupational conditions. Some agents of non-biological origin can also cause respiratory allergies. More than 250 agents are identified in scientific literature as capable of triggering the development of occupational asthma, usually by means of a specific immune response.[161,256]

Two broad categories of allergen are recognised: high molecular weight (HMW) allergens (those with a molecule weight of more than 5,000 daltons) and low molecular weight (LMW) allergens (those with a molecular weight of less than 1,000 daltons). HMW allergens are proteins or protein-like molecules, including enzymes; LMW allergens are often small chemical compounds. The most common inhalant allergens found in the workplace are listed in Table 3.1. A more comprehensive overview can be found in the publication by Van Kampen *et al*. (2000).[256]

The HMW allergens include certain mixtures of allergens responsible for respiratory allergies.[108] Flour dust and latex include tens of different allergens, each with its own characteristics (size, water solubility, allergenic potency, biological availability), present in variable concentrations.[69]

Because the specific immune system is geared primarily to the recognition and destruction of xenobiotic proteins, any inhaled protein is in theory a potential allergen. Researchers agree that such proteins cause allergies mainly by provoking an IgE-mediated immune response.[138]

The situation with LMW allergens is somewhat different. Small chemical compounds can trigger a specific immune response only if they first bind with the body's own proteins, such as serum albumin.[132,147] The ability to form such bonds is therefore a defining characteristic of all LMW allergens. Hapten-protein conjugates can induce not only IgE-mediated, but also IgG-mediated and/or cell-mediated responses.[138] Research is presently in progress with a view to identifying the predominant type of immune response to particular chemical compounds. It is already known that acid anhydrides and platinum salts provoke mainly IgE-mediated responses.[139,168]

Table 3.1 The most common inhalant allergens found in the workplace.

HMW allergens	LMW allergens
flour dust (wheat, rye, buckwheat)	acid anhydrides
enzymes (alpha-amylase, detergents)	diisocyanates
natural rubber (latex) proteins	metals and metal salts (platinum, chromium, nickel)
proteins from animal skin flakes, hair and urine	
proteins from fish, crustaceans and shellfish	reactive dyes
pollen and other plant proteins	aliphatic, cyclo-aliphatic and aromatic amines

The predominant response associated with diisocyanates is not yet clear, however[131,139,221,222]; some researchers suspect that diisocyanates mainly provoke cell-mediated responses, but in a small part of the persons with occupational asthma also specific IgE was found. Diisocyanates may also be capable of causing non-specific irritation, facilitating the provocation of an immune response.[25,26,161,224]

3.3 Characteristics of allergens

The general physical and chemical characteristics of allergens are solubility and stability; it must be relatively easy for them to find their way from the general atmosphere into the mucous membranes of the respiratory tract (possibly carried on particles, such as pollen or dust).[124,248] In addition, the allergenic proteins and hapten-protein conjugates must possess certain determinants, enabling their recognition by T and B cells and antigen-presenting cells.[121,124,248]

Proteins vary enormously in their allergenic potency. For instance, sensitisation to rat urine proteins are reported to develop in response to exposure to concentrations of only some picograms per cubic metre (pg/m^3); sensitisation to fungal alpha-amylase and latex at concentrations of some nanograms per cubic metre (ng/m^3); sensitisation to flour dust allergens, isocyanates and platinum salts at concentrations of some micrograms per cubic metre (µg/m^3); and sensitisation to acid anhydrides at concentrations of some milligrams per cubic metre (mg/m^3).[21,106] It should be recognised that the apparent variation is attributable not only to the intrinsic characteristics of the allergens concerned, but also to the test systems used (variations in the way of exposures and assessments of sensitisation), and to the specific mixtures involved (flour dust, latex).

It is not yet clear which intrinsic fundamental characteristics, besides the physical and chemical characteristics, determine the ultimate degree of allergenicity. Theoretically, it is not presently easy to predict from the properties of a substance how potent it is likely to be.[121,190] Nevertheless, a number of intrinsic factors can be identified, which influence allergenicity:

- A protein's ability to retain three-dimensional structural integrity. Structural integrity influences the effectiveness of the bond between the allergen and the associated immunoglobulin.[39]
- A protein's ability to retain its functional properties, such as enzyme activity.[248] A number of enzymes, including proteases and nucleases, exhibit a high degree of potency, one of the reasons being that they are able to cause tissue damage.[39,121,132]

- Non-specific irritation. Certain authors have suggested that the irritant properties of an allergen can amplify the immune response to it, since irritation causes tissue damage. Irritation provokes a non-specific inflammatory response, which can ultimately result in a specific immune response. Furthermore, by causing tissue damage, an irritant allergen is more readily able to penetrate the mucosal membranes, which makes it easier for the allergen to come in contact with the immune system.[26,138,248]

The allergenic potency of a protein or chemical agent can be ascertained by using animal models.[121,138] Such modelling is usually performed using guinea pigs and mice. The animals are sensitised by inhalation, intratracheal or intranasal exposure, or by intraperitoneal injection. This is followed by renewed exposure to induce elicitation. The response that follows renewed exposure can be measured. Monitored parameters will typically include the degree of swelling or lung function change. Specific IgE serum levels may subsequently be determined.[58,138,140]

An example of a test that is nowadays used to determine the allergenic potency of allergen with a low molecule weight is the so-called (modified) local lymph node assay (LLNA) technique.[257] This technique involves spreading a potential allergen on the ear of a mouse, then assessing the immune response by measuring the proliferation of lymphocytes in the drained lymph glands.[257] The LLNA is suitable not only for demonstrating the sensitising activity of LMW compounds, but also for providing information about concentration-response dependency, which cannot be ascertained from most other tests.

However, the LLNA does not distinguish between skin contact sensitising agents and respiratory sensitising agents. To make such distinction possible, it has been suggested that cytokine fingerprinting should be used in the context of the LLNA. This would involve analysing the cytokine profile induced in the draining lymph gland by the allergen in order to determine the type of response associated with the allergen.[138] However, cytokine fingerprinting has yet to be validated and the LLNA therefore remains (for the time being, at least) unsuitable as a means of assessing the nature of the immune response to a protein.

Generally speaking, none of the test methods presently available has been validated as a means of predicting the inhalatory sensitising potency of an allergen.[138]

3.4 Monitoring of airborne allergens

Allergens with a high molecular weight are often monitored using gravimetric particulate measurement techniques, which typically focus on certain particulate

fractions in inhalable dust. This involves first using filters to collect particulate material – consisting of a mixture of allergens and other agents and particles – from the atmosphere. In the occupational context, the material is collected over the course of a working day, mostly using pumps to draw air through the filters. The next step is to separate the allergens collected on the filter by extraction, so that the allergens may then be quantified by immunochemical methods. Immunochemical quantification entails the use of specific antibodies against the allergens concerned.[106,227]

A number of points should be taken into account in the context of interpretation of the collected exposure data. For instance, in practice, the way allergens are sampled and analysed varies, and this can lead to discrepancies in the levels of exposure measured for different research groups.[113,227] Apparent discrepancies in exposure may be attributable, for instance, to differences in the mixtures of allergens involved or to differences in the working conditions. By no means all the antigens in such mixtures have yet been characterised, and in practice researchers measure only one or a small number of allergens that the mixtures contain.[227] The acceptability of such variations should be considered on a case-by-case basis. Nevertheless, a comparative study of the findings of several laboratories found that, despite the existence of methodological differences, the inter-study variations in the exposure data for rat and mouse allergens and for fungal alpha-amylase were not as serious as might have been expected.[106,155]

The problems outlined in the previous paragraph can be addressed by standardising the monitoring methods used. In this regard, certain positive developments may be identified. For instance, as part of the European MOCALEX-project (Measurement of Occupational Allergen Exposure), various papers have been published containing suggestions and more detailed proposals for the standardisation of certain immunoassays for airborne allergens, such as (wheat) flour dust, fungal alpha-amylase and proteins found in the urine of rats and mice.[31,71,236]

Sometimes, allergen exposure is quantified purely by means of airborne dust measurements, since the relevant methods are in many cases standardised and easier to use than non-standardised allergen measurement techniques. Such dust level measurements serve as indirect indicators of allergen exposure. Concentrations measured in this way are useful only if the concentration of allergens in a particulate material tends to be relatively stable under comparable workplace conditions. It is known, for instance, that the allergen-dust ratio can differ from one occupation to another, and from one industry to another.[104] Again, the reliability of dust measurement as an exposure parameter should be assessed on a case-by-case basis. A comparison of three epidemiological studies, two of them performed in the Netherlands, revealed a variation factor of between two and

four for wheat flour dust allergen-total dust ratio, which may be regarded as quite modest.[104]

A number of low molecular weight allergens with, including acid anhydrides[192,274], platinum salts[174] and diisocyanates[152,197], can be measured immediately after sampling using (bio)chemical methods, such as chromatography, mass spectrometry and atomic absorption spectrometry. It is important to note, however, that where some such allergens are concerned, particularly those with a complex chemical composition, no good biological measure of exposure have been identified.

Conclusions

The remarks set out above make clear that precise measurement is not always straightforward. During the collection of data, there will always be some degree of systematic or random error. It is therefore important that researchers bear in mind the potential for variations in exposure sources, and indicate how this was taken into account in the analysis of their findings.

Chapter 4

Risk factors

A prerequisite for development of specific sensitisation and allergic respiratory diseases is exposure to an allergen. In addition to this, various other factors may influence the development of these health effects. Some of these factors are work-related, but the workplace is not the only factor involved in allergen development. For instance, there are also personal factors, such predisposition and lifestyle. Also outside the workplace, workers may experience influences from the environment. The question is what the extent is to which such risk factors influence a person's response to workplace exposure and thus the development of work-related inhalation allergies.

4.1 Work-related environmental factors

Level and duration of exposure

The level of exposure is regarded as one of the key factors influencing the development of occupational allergic airway diseases.[25] Epidemiological study reports shed light on the role of exposure level in relation to allergies associated with agents such as flour dust[68,119], alpha-amylase[120,194], laboratory animal allergens[52,110,114] and acid anhydrides.[20,192,273] Despite differences in the chosen exposure parameters (inhalable dust, certain airborne allergens, choice of isomers), diagnostic methods (questionnaires, supplementary clinical examination, immunological testing), effect parameters (specific sensitisation, lung function

change, presence of asthma and/or rhinitis) and the number of risk factors present, a consistent picture emerges: the higher the level of exposure, the more likely people are to become sensitised or develop allergic diseases.[12,15,21,22] The relationship between exposure level and risk is considered more closely in chapter 7.

A few authors have suggested that allergic sensitisation occurs at higher exposure concentrations than those subsequently required to trigger allergic respiratory symptoms themselves, but the committee does not consider this proven.[12,108]

Furthermore, some researchers have reported a positive association between the average weekly duration of the exposure and the occurrence of allergic sensitisation or the development of symptoms. For example, the prevalence of sensitisation to rat urine allergens is 31 per cent among people working with rats for more than nine hours per week, but only 13 per cent among those working with the animals for between 2½ and nine hours per week, and 8 per cent among those exposed for up to 2½ hours per week (all in the first four years after starting the job).[114] However, too few studies into the significance of exposure duration have been performed to support general conclusions as to whether and, if so, to what extent exposure duration influences the occurrence of allergic sensitisation or respiratory symptoms.

Exposure pattern

Most exposure-response relationships reported in academic literature have been calculated on the basis of air samples reflecting total exposure over the course of a working day. In practice, however, exposure depends on the nature of a worker's activities during the day. Hence, the actual exposure pattern may be characterised by a relatively constant level of exposure during the working day, or by several brief exposure peaks. These peaks may influence total exposure measurements of a whole working day. A number of researchers have published data indicating that these peak exposures has a significant influence on the occurrence of specific sensitisation and the development of respiratory allergies (as associated with flour dust, diisocyanates and hexahydrophthalic acid anhydride).[109,245,274] However, not enough is yet known to draw any firm conclusions regarding the extent to which peak exposures influence the development of allergy or exposure-response relationships.[245]

Influence of dermal exposure

Skin contact sometimes plays a role in occupational exposure to allergens. There are different scenarios conceivable: for instance, that a person becomes sensitised by skin contact, but then develops a respiratory allergy by inhalation, or that a person becomes sensitised by inhalation, and then develops a respiratory allergy by skin contact.

As such, experimental research with rats, mice and guinea pigs has yielded indeed evidence that dermal exposure can lead to specific respiratory sensitisation (and vice versa).[12,15,139] The research in question was concerned with allergens, such as natural rubber latex[226,278], diisocyanates[223,262] and trimellitic acid anhydride.[11,33,269,281] This is not a surprising finding, given that specific immune responses are systemic reactions.[139]

Also in humans, dermal exposure to diisocyanates is reported to be capable of triggering an immune response in the lungs. Nemery and Lenaerts (1993) have, for example, associated respiratory disorders in miners primarily to dermal sensitisation through exposure to 2,4-methylene diphenyl diisocyanate.[187] However, relatively little is yet known about the types of inhalation allergy that can result from dermal exposure in humans or about how such exposure influences respiratory exposure-response relationships.[12]

Combined exposure

Workers in certain professions are habitually exposed to combinations of allergens and/or of allergens and non-allergenic agents.[109] Bakers, for example, frequently experience simultaneous exposure not only to flour dust allergens and fungal alpha-amylase, but also to other enzymes and allergens from storage mites, fungi and yeasts[118]; similarly, workers caring for laboratory animals will typically be in contact with rats, mice and rabbits. Little is known about how and to what extent such combined exposure influences the exposure-response relationships for individual allergens.[109]

4.2 Personal and lifestyle factors

Genetic factors

Some people are more likely to develop allergies, as a result of the presence of unfavourable genetic factors.

An example is atopy. The EAACI and World Allergy Organization define atopy as follows: ‘Atopy is a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis, or eczema/dermatitis’.[82,128,129] The allergens associated with atopic responses are everyday agents, such as proteins from dust mites and grass pollen. As the above definition indicates, atopy is not an illness, but a predisposition, which manifests itself in the form of response to environmental factors.[171]

There is presently no reliable test for atopy. In practice, however, a positive skin prick test or the presence of specific IgE test to an everyday allergen, or an elevated total IgE, is often taken to be indicative of atopic status. However, such a result is in fact indicative only of sensitisation to the allergen in question, and not of atopy itself. Hence, epidemiological research findings regarding atopy are difficult to interpret. Depending on the test criteria applied, the selected population group and the environmental factors present, it is estimated that 30 to 40 per cent of the general population are sensitised to a common allergen[108,137]; data from the European Community Respiratory Health Survey – in which sixteen countries participate, including the Netherlands – suggest that the prevalence of atopic sensitisation is in the range of 16 to 45 per cent (specific IgE level higher than 0.35 kU/L).[40]

Atopy is suggested to be a risk factor for the development of respiratory allergies triggered by HMW allergens, such as the allergens associated with the baking industry[68,118-120,194,213], latex allergens[10] and laboratory animal allergens.[77,108-110,245] Heederik *et al*. (2001) performed a sophisticated statistical analysis and calculated, for example, that atopic people (defined as those with a total serum IgE level above 100 kU/L) were nearly 1.5 times more likely to become sensitised to flour dust than non-atopic people.[107] Researchers investigating the relationship between atopy and sensitisation by LMW allergens, such as acid anhydrides and diisocyanates have either found no association[25,108,174,245] or have reported contradictory results.[192,273]

Atopy is not seen as a good predictor of specific sensitisation or of the development of allergic symptoms, because a high proportion of atopic people are not sensitised by exposure to work-related allergens and do not develop allergic symptoms.

In recent years, increasing attention has been given to the possibility that genetic factors other than atopy may influence allergy development. Such factors involve differences in genes that are somehow associated with allergic immune responses, or are thought to play a role in the development of asthma. Differences in genes that are associated with the biotransformation of agents can also

contribute to an elevated risk of allergic sensitisation and symptom development, according to some researchers.[126,166-168] However, no valid genetic markers have yet been developed, which would make it possible to study the influence of the different genetic factors on the exposure-induced respiratory allergies.

Smoking

Most epidemiological researchers have treated smoking as a lifestyle factor, but it can also be considered an environmental factor. Smoking has been found to be positively associated with the development of some work-related allergies.[25,108,191,218,241] Examples include allergies to platinum salts[174] and tetrachlorophthalate anhydride.[263] However, researchers have found no association between smoking and allergies to certain other agents, such as flour dust[118,119], alpha-amylase[120,194], laboratory animal allergens[110], diisocyanates and certain acid anhydrides.[20,68,192,273] Smoking's influence on the development of asthma may depend on the type of allergen involved and on the person's genetic status.[108,263]

Other personal risk factors

There has been little reported research into the influence of non-specific bronchial hyperresponsiveness status, age, ethnicity or gender on the development of respiratory allergies.[118-120] However, it is not clear whether bronchial hyperresponsiveness status is an independent risk factor, or a consequence of asthmatic status.[171] Not enough is known about the other factors to support any conclusion regarding their influence on occupational allergic respiratory disorders.[19,108]

4.3 Other environmental factors

Cross-reactions

A cross-reaction involves a specific antibody attaching an antigen other than its target antigen. Cross-reactions usually involve allergens that are structurally very similar (*i.e.*, similar in terms of amino acid sequence and three-dimensional structure), but not always. Cross-reactions involving both HMW and LMW allergens have been observed, such as that between latex and certain types of fruit (kiwis, bananas, chestnuts and avocados; 'latex-fruit syndrome')[69], those between flour dust allergens from various taxonomically related grain species[108,118], and those between various diisocyanates.[108] Amylases, however, are rarely associated with cross-reactions.[108,118]

To what extent cross-reactions influence the exposure-response relationships of certain allergens is unknown.

Exposure to dust particles

Air can contain solid or liquid particles resulting from, for example, mechanical processes, condensation and/or re-suspension. There is a danger of them acting as carriers for harmful agents, such as allergenic proteins, thus facilitating the passage of such agents into the respiratory tract. The part of the respiratory tract at which an allergic symptom develops depends on the size of the particles and the effort being made by the worker at the time of inhalation: the greater the effort the deeper a worker will breath.[108]

It is unknown to what extent dust particles influence the exposure-response relationship of a certain allergen.

Adjuvants

Chemical agents can contribute to the development of allergies by stimulating the immune system or by increasing effective exposure.[108,191,218,258] An agent that has such an effect is referred to as an adjuvant. If, for example, an agent influences the way an allergen bonds with cells, or increases the activity of antigen-presenting cells, or interferes with the balance between the various types of T-helper cell, the specific immune system will be stimulated more than otherwise. As a result, fewer allergens are required to provoke a given specific immune response. Adjuvants include air pollutants, such as ozone, oxides of nitrogen, and particulate materials from diesel fumes and tobacco smoke.[98,151,185,205,258] Certain detergents, disinfectants (quaternary ammonium compounds)[218] and phthalate plasticisers (which make plastics flexible) are also suspected of stimulating the specific immune system. It is believed that simultaneous combined exposure may be needed for an adjuvant effect to occur.

Irritants form a subgroup of adjuvant agents. Substances with irritant properties can increase effective exposure to an allergen by damaging the epithelium of the respiratory tract.[108] In this way, they can influence the development, seriousness, duration and nature of an allergic response, and can contribute to asthma-like responses and inflammation of the respiratory tract.[12] Irritants include not only non-allergens, such as tobacco smoke, nitrogen dioxide and soot particles, but also most LMW allergens, such as diisocyanates and acid anhydrides, which possess both allergenic and irritant properties.[12]

The influence of irritants can complicate interpretation of allergenic responses to different levels of exposure. Research indicates that the exposure concentration required to cause irritation is probably higher than that required to provoke an allergic response, but evidence for this is hardly available.[12]

Infectious agents

There is a significant body of published evidence that viral infections can influence the emergence and subsequent course of allergic disorders.[19,57,80,81,122] For instance, it is known that rhinoviruses (common cold viruses) stimulate the allergenic response.[81,122] Furthermore, researchers found that intranasal inoculation of volunteers with a RV39 common cold virus triggered a rise in total serum IgE concentration among subjects who suffered from allergic rhinitis, but not among those who did not.[242] It has also been suggested that microbial infections, *e.g.* involving bacterial cell wall components such as endotoxins, may be influential.[122,158,159,233] However, further research is needed before firm conclusions may be drawn regarding the clinical relevance of viral infections or their influence on the emergence and subsequent course of allergic disorders. So far, the explanations given for these observations are that bacteria of viruses cause local tissue damage and inflammation, and probably also interfere with the specific immune response.[42,57,81,108,122]

On the other hand, some researchers have postulated the existence of an association between underexposure to bacteria, viruses and parasites and the increased prevalence of allergic illnesses.[17,30,102,217] However, the findings of research into this 'hygiene hypothesis' are as yet inconclusive.
At this moment it is not clear to what extent infectious agents can influence the exposure-response relationships of allergens.

4.4 Conclusions

On the basis of the considerations set out above, the committee concludes that certain risk factors are clearly associated with the development of allergies. However, it remains unclear how much influence these factors have on the induction of sensitisation and the development of allergy (caused by occupational exposure), simply because not enough is yet known. Nevertheless, the identification of such additional risk factors is important not only for the proper assessment of proposed occupational exposure limits, but also for the acquisition of a good overview of the risk factors that exist. Such factors can then be taken into account when seeking to improve working conditions.

Chapter 5

Prevalence in the working population

This chapter considers the prevalence of allergic sensitisation and occupational respiratory allergy in certain occupational groups. First, the strength of the available research data is examined. In order to put the occupational statistics into perspective, data on the prevalence of allergic sensitisation and respiratory disorders in the general population are also presented.

5.1 Strength of the available research data

Research data are needed to define an association between workplace exposure to allergens and work-related sensitisation and respiratory allergies. Various methods can be used to identify an association, each with its own advantages and disadvantages. Failure to take sufficient account of differences in the strength of different forms of evidence can compromise interpretation, leading to the incorrect definition of associations or to under or over-reporting.

Problems with collecting and interpreting response data

Nearly all data concerning occupational allergic respiratory disorders come from observational research and, where some allergens are concerned, from interventional research. The object of observational research is to describe a particular situation as accurately as possible, without exerting any influence of the researcher on the situation in question and thus incorporating the effects of that

influence into the findings. Such research is very valuable in finding an association between exposure and response.

Where observational data are used, the main danger is the introduction of systematic measurement errors, such as selection bias, information bias and confounding bias. Furthermore, if the selected study population is too small, it is possible that differences in health effects will be overlooked.

Regarding selection bias, this involves the selection of a study population and study conditions that are not truly representative for the group of workers with whom the study is concerned. Another form of selection bias is the healthy-worker effect: the selection of a study population that is misleadingly healthy, because for instance unhealthy workers have left the workplace in the setting concerned. This phenomenon is particularly of importance in the interpretation of cross-sectional studies, since they involve the collection of data at one particular point in time.

Information bias occurs if exposure is not measured properly, or if diagnosis is imprecise. It also occurs if data are compared that are collected from different studies. Imprecise diagnosis may involve some cases of illness going unrecorded or similar illnesses being erroneously grouped together. To establish whether exposure to an agent causes work-related asthma, for example, it is necessary to distinguish between new-onset asthma (asthma that a previously healthy worker develops at work) and work-aggravated asthma (a pre-existing or latent allergy made worse by occupational exposure).[23,250] Studies that rely solely on questionnaires to quantify illness cases frequently arrive at higher prevalence figures than studies that also use clinical diagnosis.

Confounding bias is said to exist when an effect of one determinant is mistaken for an effect of another determinant. This may cause problems in associating disease causes to certain determinants. If, for example, workers are exposed to two allergens in combination, study of either allergen's effect will be confounded by the presence of the other.

Nowadays, researchers take into account for the occurrence of systematic errors by using predefined procedures and power analyses. However, such tools were not available in the past, and even now insufficient account is sometimes taken of the scope for measurement errors.

The most reliable observational data are those obtained from systematic epidemiological studies, such as prospective cohort studies, in which people are monitored for a period from the start of their working life, and in which the criteria used are as precisely defined as possible and are validated. Unfortunately, such studies are time-consuming and expensive; as a result they are relatively scarce.

Unlike observational research, interventional research involves the investigator acting to influence the situation being studied. Interventional research is a form of experimental research, which is used mainly to establish whether a preventive measure, such as the cessation of exposure, has any effect on the prevalence of a condition. Such research can also demonstrate that exposure was the cause of the condition.

Conclusions

All things considered, it is inevitable that the collection of data will introduce a degree of measurement error. Provided that the degree of error is within certain limits and proper critical account is taken of it, its existence need not invalidate any subsequent findings. However, it is important to recognise, for example, that prevalence data can be under- or over-estimated. Also, due to measurement errors results among comparable populations can vary when they are compared.

5.2 Prevalence in the general population and the wider working population

General population

The National Public Health Compass reported that roughly 14 to 18% of adults in the Netherlands suffer from asthmatic symptoms, such as shortness of breath and a respiratory whistle.[45] The number of adults that have ever suffered from asthma is estimated to be between 3 and 5%. These figures come from two Dutch studies: the ELON study (European Respiratory Survey in the Netherlands, 2000) and the MORGEN project (Monitoring of risk factors and health in the Netherlands, RIVM, study period 1993-1997). Both studies used questionnaires to collect data. The questionnaire-based surveys were backed up by lung function tests, bronchial hyperresponsiveness measurements (ELON), skin prick tests (ELON) and serological tests for total and specific IgE associated with everyday allergens, performed on a small part of the survey population. The ELON study found that half of people aged twenty to twenty-nine and a quarter of people aged sixty to sixty-nine were affected by allergic respiratory disorders (as determined from total and specific IgE concentrations in the blood). Most of the allergies concerned were to dust mites (25%), timothy grass (17%), birch (12%) and cats (7%). Unfortunately, no reliable data are available concerning rhinitis or rhinoconjunctivitis, although data regarding infections of the upper respiratory tract are available.[16]

Estimates vary as to the extent to which the prevalence of asthma within the general population is attributable to the working population.[168] The reason being that much depends on the way asthma is defined, the composition of the study population and the research methods used.[28,168] No Dutch data are available concerning the amount of asthma attributable to occupational exposure. In the USA, however, the American Thoracic Society (ATS) published, in 2003, well-analysed estimates.[18] In the article work-related asthma is interpreted as clinically diagnosed allergic or non-allergic asthma known to result from occupational exposure. In this instance, the PAR was the percentage (attributive fraction) of the incidence in the general population that is attributed to occupational exposure. Looking at twenty-one separate studies, including cross-sectional, cohort and case control studies, the median value of PAR was found to be 15% (range 4 and 58%).

A few years earlier, Blanc and Toren published attributive fraction data based on no less than forty-three separate studies, some of which were also used by the ATS.[28] These researchers arrived at a median value of 15% for the proportion of asthma cases attributable to work-related factors. A Finnish study not considered by Blanc and Toren arrived at an attributive fraction of 29% for men and 17% for women.[133] Finally, data are published recently on the European Community Respiratory Health Survey, in which 13 countries participate.[142] The data show that the extent of asthma in the general population that is caused by occupational exposure, varies between 10 and 25%. This is equivalent to an incidence of new-onset occupational asthma of 250 to 300 cases per million people per year.

Wider working population

Most estimates of the prevalence of work-related (allergic) respiratory disorders in the working population are derived from epidemiological research and from reporting or registration systems. It would of course be interesting to know what proportion of these asthma cases was actually attributable to occupational exposure.

Various authors have made the assumption that most cases involve allergic asthma, but it is difficult to provide exact figures. Researchers have reported that in Canada no less than 90% of financial compensation claims for asthma arise out of allergic sensitisation to an agent used in the workplace.[251] The committee is inclined to regard this as an overestimate, however, since in many countries compensation claims are usually honoured only if they involve allergic asthma. No reliable data are available concerning the situation in the Netherlands. However, researchers have estimated that, in the Netherlands, between five hundred and

two thousand new cases of asthma a year probably occur as a result of occupational exposure.[108] These figures make use of incidence data from other countries, coupled with data on the size of the Netherlands' working population (about seven million).

Data on the prevalence of work-related rhinitis and rhinoconjunctivitis in the Netherlands' wider working population are available from various sources. However, comparison of the sources in question is not straightforward, since the supporting studies differed considerably in the way they were set up. Working from general population survey data and assumed PARs, the RIVM estimated in the context of an exploratory study that 30% of all cases of rhinitis (and sinusitis) in the active working population were attributable to workplace exposure.[16] Considerable uncertainty is attached to the RIVM figure, however, since it was calculated on the basis of various extrapolations and assumptions. Furthermore, there are no data on the amount of allergic rhinitis attributable to work-related exposure. Another source of Dutch prevalence data is the Netherlands Centre for Occupational Diseases. They publish information collated from the National Register of Occupational Diseases.[181] Tens of new cases of (allergic) occupational asthma and rhinitis are recorded in the register each year. The register is not comprehensive, however, so the number of recorded cases may tend to underestimate the true figure. Furthermore, no attempt is made to verify the diagnosis.

5.3 Prevalence in certain occupational groups

In the workplace more than 200 allergens are identified. For practical reasons, in this section only a few high risk occupational groups are evaluated. More information can be found in comprehensive reviews, such as those published by Heederik *et al*. (1999, see also Annex D of this report) and Siracusa *et al*. (2000).[108,241]

Baking and flour-processing industry

In the mid-1990s, rounded-down about 50,000 people were employed in the Netherlands' baking industry and other flour-processing industries (source CBS and NBS, 1993/1994). Of these people, roughly 30,000 were directly exposed to potential allergens in the form of flour dust and/or the enzyme fungal alpha-amylase.[108,117,171] The committee emphasises that the number of people employed in the industries concerned is subject to fluctuation.

Allergic sensitisation. On the basis of reported cross-sectional study data and their own findings, Houba *et al*. (1996, 1998) calculated that between 5 and 28%

of baking industry workers were sensitised (by IgE mediation) to wheat and/or rye flour dust, and 2 to 16% to fungal alpha-amylase.[117,118] Subsequently published separate cross-sectional studies confirm this finding.[38,67,171,195,268] From the available data, it would also appear that the prevalence of specific sensitisation is influenced by the level of exposure[119] and by atopic status.[67,119,120] One Dutch study, for example, found that in a group of 346 bakers, the prevalence of sensitisation to flour dust allergens (specific IgE) ranged from a little over 4% in the lowest exposure group to 14% in the highest exposure group.[119] Among atopic people, prevalence in the highest exposure group was nearly 23%; while among non-atopic bakers it was 11%. In the context of this study, a person was considered atopic if his or her total serum IgE level was more than 100 kU/L and if he/she tested positive for IgE specific to at least one everyday allergen (*e.g.*, dust mites, grass pollen).

Respiratory disorders. Third-party review of various cross-sectional studies from different countries has revealed a relatively wide spread in the prevalence figures obtained for asthma and/or chest disorders (from 5 to 14%) and for nasal/eye disorders (from 14 to 29%).[117,118] The variance is caused by factors such as differences in research methodology and in the way disorders are diagnosed. The percentages quoted cover both disorders caused by immunological mechanisms and those caused by non-immunological mechanisms, since it was not possible to demonstrate IgE-sensitisation in all cases. It is worth noting that some authors have reported even higher prevalences. A Norwegian cross-sectional study, for example, put the prevalence of occupational rhinitis at between 23 to 50%, depending on the criteria applied.[249]

In the Netherlands, the findings of a study of allergies to raw materials among 391 baking industry workers indicated that the prevalence of work-related asthma was 11.5%, and that the prevalence of rhinoconjunctivitis (with normal lung function) was 18%.[195] Higher prevalences were found among bakers who appeared to have been sensitised to one of the specific workplace allergens (flour dust, alpha-amylase: more than 50% for asthma and 34% for rhinitis).[107,119,195] These figures imply that some bakers have respiratory disorders, but that among them no IgE-sensitisation could be detected. Dutch research also indicates that greater exposure leads to a higher prevalence: 15.4% of workers in the lowest exposure group suffered from a combination of rhinitis and shortness of breath, while 28.7% of those in the highest exposure group had such problems.[107,119,195]

From these data, it is clear that allergic sensitisation and respiratory disorders associated with allergens specific to the baking industry are commonplace. Fac-

tors such as atopy and the height of exposure increase the risk of a worker developing an occupational respiratory allergy.

Animal care facilities

In the Netherlands, an estimated 4,600 people are exposed to allergens from laboratory animals, such as rats, mice and insects (fruit flies).[171] If people involved in the breeding of such animals are included, the number is greater. Also here, the committee emphasises that the number of people employed in the industries concerned is subject to fluctuation.

Allergic sensitisation. The prevalence of specific sensitisation among newly started laboratory animal workers – as determined by means of skin prick tests with urine allergens or skin flake allergens from various laboratory animals (mice, rats, rabbits, guinea pigs and hamsters) – has been put at between 16 and 24%, depending on the type of allergen concerned.[52,75,114,154,228]

A Dutch study put the prevalence at about 10%, on the basis of IgE testing (IgE ≥ 0.7 kU/L for rat urinary protein allergens).[110,114] Atopy apparently increases the prevalence of specific sensitisation (by about a factor of three) compared to non-atopics, as does higher exposure.[52,75,110]

Respiratory disorders. In the UK, it is estimated that about 5% of all cases of work-related asthma are caused by exposure to laboratory animal allergens.[96] Given the relatively small number of people employed in this industry, that is a high percentage.

The prevalence of laboratory animal allergies (eye, nose, skin and/or asthmatic symptoms) among Dutch workers is estimated to be between 11 and 44%.[114,115,264] Non-Dutch prevalence figures for (allergic) occupational asthma resulting from exposure to rodents are broadly consistent.[25,41,76,154] In an estimated 30% of these cases, the people concerned have raised concentrations of specific IgE against rat urine proteins in their blood.[154] The prevalence of asthma associated with exposure to fruit flies is reported to be 32% and that associated with exposure to locusts to be between 14 and 26%.[171]
Among laboratory animal workers, the prevalence of non-specific rhinitis and rhinoconjunctivitis is put at 42 to 80%[41,231] and that of work-related rhinoconjunctivitis at 24%[229] The prevalences of work-related (IgE-mediated) allergic rhinitis and rhinoconjunctivitis confirmed by immunological testing are lower, however, at between 6 and 10%.[78,229,231]

Various studies have suggested that atopy and the duration and level of exposure increase the risk of developing allergic respiratory disorders in response to exposure to laboratory animal allergens.[78,110,228]

Sectors in which latex containing gloves are used

Natural rubber, or latex, comes from the rubber tree (*Hevea brasiliensis*).[69,108] Latex protein allergens can associate with powder (typically starch) due to the physical drying process in manufacturing. Latex contains dozens of proteins that can cause allergy.[272] When latex gloves are donned and removed, airborne latex allergens can enter the air. Latex gloves are widely used in health care and in laboratories (by nurses, doctors, dentists, laboratory technicians, etc.), to protect against microbial agents and so forth. Other occupational groups, such as hairdressers and food handlers, also use them. It is not known exactly how many people in the Netherlands are occupationally exposed to latex allergens, but the figure is likely to be several hundred thousand.[108,244] Last years there is growing awareness of the adverse health effects that may be encountered by the use of these gloves.

Allergic sensitisation. US data indicate that the prevalence of specific sensitisation in the general population were generally reported as between 2 and 12%, and as high as 25% in some populations.[51,69,244,253,272] The findings should be interpreted with caution, since the various studies used different skin prick and serological test techniques, and the study populations were not entirely comparable. In the Netherlands, the prevalence of sensitisation among health care workers has been put at between 2 and 17%.[108,270]

Respiratory disorders. Little is known about the prevalence of allergic disorders associated with latex. It is estimated that approximately 0.5% of cases of allergic rhinitis in the working population are attributable to latex.[108] Estimates of the prevalence of occupational asthma among health care workers vary between 2.5 and 11%; for rhinitis the figure has been put at 13%.[108,244,270]

In recent years, a great deal of effort has been made to reduce the number of latex allergy cases, by preventive action. This has reduced the incidence of new cases. For instance, Allmers *et al.* (2002) reported a steady decline in latex-related asthma among health care workers over the period 1996 to 2002, brought about by improved information dissemination and the use of powder-free low-protein gloves.[4] The same research group had previously observed a sharp drop in latex-specific IgE levels among personnel that had raised concentrations prior to the switch.[3]

Bell pepper and flower horticulture

An estimated 7,000 to 8,000 people work in the Netherlands' bell pepper cultivation industry. Groenewoud *et al*. (2002, 2005) have recently published the results

of a cross-sectional study into the prevalence of occupational allergies among Dutch bell pepper and flower greenhouse employees.[100,101] More than 35% were found to be sensitised (SPT) to one or more bell pepper plant allergens (27% to capsicum pollen). The prevalence of work-related respiratory disorders was 54%. About 13% of subjects suffered from asthma, 50% from rhinitis and 30% from conjunctivitis. Of the people with work-related disorders, 55% were also found to be specifically sensitised. Furthermore, 84% of the people who were specifically sensitised suffered work-related ailments. Work-related allergies were more common not only among specifically sensitised individuals, but also among subjects who were atopic (*i.e.* who registered a positive skin prick test result for at least one common inhalant allergen).

A study of 104 people working in the chrysanthemum cultivation greenhouses found that 20% were sensitised to chrysanthemum pollen (SPT).[99] Roughly half of these sensitised individuals also returned positive specific IgE test results. Eight percent had lower respiratory tract disorders (including shortness of breath), and 53% had upper respiratory tract disorders (including rhinitis and conjunctivitis). Of the people with work-related disorders, 29% were also specifically sensitised, and 81% of those who were specifically sensitised also had work-related disorders. Specific sensitisation was the principal determinant of allergic disorders of the upper respiratory tract; atopic status, duration of exposure and smoking habits did not appear to be associated.

Industrial enzymes

Industrial enzymes are used in numerous, extremely diverse sectors of the economy. For instance, since the 1960s, enzymes have been incorporated into detergents and other cleaning products. The enzymes in question include proteases, lipases, amylases and cellulases. Across the entire working population of the Netherlands, it is estimated that up to several tens of thousands of workers are exposed to one or more of these enzymes.[105] Also here, the committee emphasises that the number of people employed in the industries concerned is subject to fluctuation.

In the 1970s, three mutually independent studies produced findings indicating that roughly 40% of people working in detergent and cleaning agent production were sensitised to one or more of these enzymes and that about 15% had respiratory disorders.[157,243,271]

The industry sought to address this issue by taking various exposure control measures, one concerning encapsulation of enzymes. However, a Finnish cross-sectional study found that, even after the introduction of preventive measures,

22% of workers were sensitised (specific IgE) to the enzymes used in the factory. All the sensitised workers had symptoms of rhinitis and one also had symptoms of asthma.[261]

In a Danish retrospective follow-up study covering the period 1970 to 1992, it was discovered that 36% of more than a thousand subjects were sensitised to a protease (protease-specific IgE RAST > 0.5 Sorbent Units (SU)); 8% actually had a specific IgE RAST of more than 2 SU (≈ 0.70-3.49 kU/L).[130] Five percent of subjects suffered from asthma caused by exposure to enzymes and 3% from rhinitis attributable to such exposure. Half of the workers who developed allergic disorders did so within fifteen months of exposure starting. More recently, new data were presented from the same enzyme producing plant.[149] Of the 1,207 employees from which pre-employment data were available, 27% developed enzyme-related sensitisation, and 6.4% enzyme-related allergy. All the workers with enzyme-related allergy also were sensitized to those enzymes. The median follow-up time was 2.5 years. Authors state that data may have been underestimated, due to implementation of preventive measurements to lower exposure, and the fact that until 1980 atopics were not allowed in the workplace.

Researchers in the UK reported the findings of a cross-sectional study performed in 1998, which looked at the workforce of a detergent factory. Skin prick tests for the enzymes used at the factory revealed sensitisation in between 15 and 26% of the 350 subjects, depending on the type of enzyme in question – despite the fact that encapsulated enzymes were used.[53] Across the various activity groups, an average of 19% of workers not only suffered from work-related respiratory disorders, but also registered positive specific skin prick test results. The highest prevalences (in excess of 50%) for specific sensitisation and respiratory disorders were found among re-fillers.

Industries using diisocyanates

Diisocyanates have a wide variety of applications, in the context of which an estimated 15,000 people are occupationally exposed to these agents in the Netherlands.[245] The most extensively used diisocyanates are toluene diisocyanate (TDI), diphenyl methane diisocyanate (MDI) and hexamethylene diisocyanate (HDI) monomers.[221,222] Diisocyanates are used as raw material in the synthesis of polyurethanes. These are used for the production of foam rubber, plastics, synthetic resins, adhesives and glues, paints and varnishes. For certain occupational groups it is unknown how many people are actually exposed to these diisocyanates.

In the scientific literature, asthma prevalences of between 1 and 20% have been attributed to exposure to diisocyanates.[48,108,197] Among people with occupational asthma caused by diisocyanates, 10 to 30% have been found to carry specific IgE; in cases of occupational asthma caused by other isocyanates, no specific IgE was found.

The above figures relate to exposure to monomers, whereas mixtures of oligomers are now in increasing use.[221,222] However, more recently, data concerning exposure to oligomers have been published. These data – from a Dutch study of people working in paint spray shops – show that the prevalences of COPD (26%) and asthma-like disorders (33%) among spray painters were significantly elevated, compared with the prevalences (8 and 14%) among a control group made up of office workers. The asthma disorders were strongly associated with objective measures, such as bronchial hyperresponsiveness. A higher prevalence of rhinitis was also detected, but the difference was but not statistically significant (20% versus 14%). The proportion of subjects exhibiting IgE sensitisation to both monomers and oligomers was very low, however (no more than about 4%). IgG sensitisation was clearly more common in spray painters, of whom up to about 50% tested positive for certain types of specific IgG. Among the office workers, no specific IgE sensitisation was found and specific IgG sensitisation was significantly lower.[221,222]

Regarding diisocyanates, research is in progress, for instance on the reliability of certain exposure parameters, such as specific IgG binding, and on the best way in determining asthma caused by diisocyanate exposure.[27,43,199,277]

Industries using acid anhydrides

It is estimated that at least a thousand people in the Netherlands are occupationally exposed to acid anhydrides.[245] Acid anhydrides are used, for example, as hardeners in the synthesis of epoxy resins.

Allergic sensitisation. Figures for the prevalence of work-related sensitisation to anhydride conjugates vary from about 13 to 38% (for specific serum IgE and/or IgG) and from about 8 to 17% (for SPT with serum albumin anhydride conjugates).[156,192,273] No specific sensitisation to these agents was detected in unexposed people. Greater exposure and atopy were found to increase the likelihood of specific IgE-mediated and/or IgG-mediated sensitisation.

Respiratory disorders. Among people occupationally exposed to acid anhydrides, the prevalence of occupational asthma was up to 30%.[108] Similar prevalences of nasal disorders have been reported.[192] The importance of the role played by allergy is not entirely clear, but 40 to 100% of people with occupational

asthma who worked with acid anhydrides also tested positive in one of the immunological tests for sensitisation to anhydride conjugates[108]; for nasal disorders, a corresponding figure of 30 to 49% has been reported, and a figure of 62 to 85% for nasal haemorrhage.[192,273]

There is considerable spread in the prevalences quoted for acid anhydrides. This is attributable partly to differences in exposure level, in the type of anhydride and in the nature of the industrial use.

5.4 Quality of life and disease burden

It will be clear from the foregoing that a substantial proportion of people who are occupationally exposed to allergens become specifically sensitised. Some of them also suffer from respiratory allergies. It is important to consider the implications of this for the quality of life and disease burden of the people concerned. This issue has attracted increasing attention in recent years, because of the potential socio-economic consequences.

Quality of life

Various studies have demonstrated that allergic illnesses can diminish quality of life, at both the personal and socio-economic levels.

At the personal level, such illnesses can influence the ability to function normally both at work and in the context of physical, psychological, social and domestic activities.[34,111,144,153] Sufferers can experience problems varying from sleep impairment resulting in fatigue, rhinitis-related thirst, concentration problems and headache, practical problems such as the need to always carry tissues because of rhinitis, the need for frequent nose-blowing and emotional problems.[111,153] Asthma sufferers tend to experience physical impairment, while rhinitis sufferers are primarily troubled by psychological affects.[111]

At the social level, the principal effect is (temporary) work disability. Work disability manifests itself through absenteeism, reduced productivity, the need to change jobs and withdrawal from the labour market. No precise data are available concerning the amount of absenteeism in the Netherlands that involves people with work-related (allergic) respiratory disorders. However, some research have been performed to study the effects of airway symptoms on absenteeism and absence in groups of workers.[2,220] From these data, the researchers concluded that workers having airway symptoms had higher sickness absence. Regarding asthma, researchers in other countries have found that absenteeism is higher among asthmatics and rhinitis sufferers than among healthy people, and that such

people are less productive.[29,70,260] A British study report indicated that a worker with occupational asthma is off sick for between about two and ten working days a year, depending on its seriousness.[35] It should be noted that absenteeism is rarely attributable to a single cause; several factors usually play a role.[32]

Many asthma sufferers move to other jobs with their existing employers or, if that is not possible, seek employment elsewhere.[7,29,37] According to non-Dutch researchers, some ultimately find themselves unemployed. However, the unemployment problem is difficult to quantify with any confidence, because of a paucity of reliable data and because it is difficult to separate the effect of work disability from the effects of other occupational and socio-demographic factors (such as unskilled work, educational status and age).[7,29,37,70,260] Furthermore, direct extrapolation to the Dutch situation is not appropriate, because of differences in the applicable compensation arrangements and so forth. In the literature one finds suggestions that asthma sufferers are more likely to become unemployed, while rhinitis sufferers tend to remain in work but become less productive.[29,260]

In the Netherlands, a study was recently undertaken to ascertain the number of people entering state disability benefit schemes as a result of work-related respiratory disorders in the period 1998 to 2000, inclusive.[143] No distinction was made between work-aggravated disorders and work-induced disorders. Some 1.9% of new benefit claims was attributable to respiratory disorders; of these, more than a third (37.1%) were work-related. Asthma accounted for about 11% of the respiratory disorders, and 46% of the surveyed asthma sufferers considered their condition to have been caused by their work.

Occupational allergic airway disorders have irreversible consequences for the economy. Various direct cost items arise out of these disorders, principally medical consultations, use of care facilities and consumption of medication and therapies. There are also indirect costs, such as the loss of income associated with absenteeism and reduced productivity, and lower pay attributable to the need to find alternative (lower-status) work and full or partial unemployment.

In 2000, direct medical costs attributable to all forms of asthma amounted to roughly 141 million euro's in the Netherlands; of this sum, the medication bill accounted for more than 76 million.[116] The average expenditure per patient in that year was 313 euro's. No Dutch data on the indirect costs associated with asthma are available, but information from a European survey indicates that more than half of all such costs are due to lost productivity.[160] The data do not provide any insight into the cost of work-related (allergic) respiratory disorders. Nor have any thorough cost analyses been performed for (allergic) rhinitis.[225]

Estimates of disease burden

Disease burden, that is to say the extent to which the health of a population is adversely affected, is quantifiable. Various indicators of disease burden are used. In the health care sector, the term QALY (quality-adjusted life-year) is used.[144] A QALY represents a year of life in full health, and points to 'health benefit'. In the environmental policy domain, a related indicator is used: the DALY (disability-adjusted life-year).[89,175,176] A DALY is a year in full health that is retained, which indicates 'avoidable disease burden'. Both indicators take account of lifespan and any positive or negative change in health status. Both the QALY and the DALY can be used to analyse the influence that environmental factors, such as exposure, or intervention measures have on health.

Disease burden data can also be used in cost-effectiveness analyses: the cost per QALY gained or per DALY lost may be calculated for a given intervention measure, thus shedding light on the benefits (effectiveness) and undesirable consequences (cost) of the relevant course of action. The Health Council has recently evaluated the suitability of these two indicators, and of a third indicator, for use in the context of health-based environmental policy.[89] Both the QALY and the DALY are considered suitable for the estimation of (avoidable) disease burden.

For the Netherlands, impact statistics expressed in DALYs are available for very few disorders, and allergic respiratory disorders are no exception in this regard. The RIVM has made a rough estimate of the disease burden on the working and formerly working population resulting from workplace exposure; the asthma-related burden appears to be about 1,400 DALYs (uncertainty margin 280 to 7,000), and the rhinitis and sinusitis-related burden about 4,230 DALYs (uncertainty margin 800 to 21,000).[16] The rhinitis and sinusitis-related burden is primarily attributable to infection. The asthma-related disease burden on the general population is believed to be more than 27,000 DALYs. The disease burden estimates for asthma and rhinitis are accounted for largely by health impairment; the disorders are not thought to be responsible for any significant amount of premature mortality.

Worldwide, the total loss of DALYs due to respiratory disorders arising from occupational exposure is put at 6.6 million (breakdown: COPD 56%; asthma 25%; pneumoconiosis 19%). In Western Europe, the corresponding figure is 324,000 DALYs (breakdown: COPD 63%; asthma 17%; pneumoconiosis 20%).[66]

5.5 Conclusions

In certain industries, the risk for developing allergic respiratory symptoms due to occupational inhalation of allergens is relatively high. These include people working in the baking and flour-processing industries, laboratory animal care, and the bell pepper and flower greenhouse cultivation industry, as well as people who are exposed to industrial enzymes, soluble platinum salts, isocyanates or acid anhydrides at work. Epidemiological data from these types of industries suggest that the risk may amount to several dozen percentage points, depending on the type of allergen and other factors. Hence, a substantial proportion of workers who are exposed to airborne allergens at work develop specific sensitisation and allergic respiratory diseases.

The disease affects the quality of life and adds to the disease burden among the working population.

Chapter 6

Sensitisation as basis for recommended OELs

For the derivation of recommended occupational exposure limits data are needed on the height of exposure, and on the effect that is considered the most critical one. Concerning the latter, the limit not only can be based on an adverse health effect that is first observed when raising exposure, but also on an effect that represents a crucial event in disease development. This chapter evaluates the critical effect for allergens.

6.1 Allergic sensitisation or airway symptoms?

The development of an allergic respiratory condition is always preceded by sensitisation for a particular allergen. Sensitisation is an early health effect, which causes changes in the immune system and often also permanent hypersensitivity to a particular agent. Once these changes take place, a person is liable to develop a respiratory allergy. In this regard, the process of allergy development is quite unlike most toxic effects, which do not entail changed hypersensitivity.

Observations show that when exposure is continued after becoming sensitised, in a relative short time, the number of workers who develop allergic respiratory symptoms may amount to several dozen percentage points (see Table 2.1). The committee, therefore, assumes for safety reasons that with continued exposure almost every worker, who is sensitised, is likely to develop an allergic respiratory disorder.

In short, the occurrence of allergic sensitisation is a critical point in and a prerequisite for the development of an allergy. In view of these biological considerations and on the assumption that a considerable number of sensitised workers will ultimately develop allergic airway symptoms, it is reasonable to believe that OELs based on allergic sensitisation data – and not on symptom data – provide the best protection against the development of inhalant allergies.

6.2 Remarks

The use of sensitisation as the critical response in the context of occupational exposure limit calculation raises certain issues. A question is for example how effective an occupational exposure limit based on sensitisation would be. Research data, particularly from cross-sectional studies, appear to indicate that not everyone suffering from a respiratory condition attributable to exposure is in fact sensitised for the allergen. This is not strictly relevant, however. For one thing, biologically speaking, anyone who has an *allergic* respiratory condition is by definition sensitised. The fact that this is not backed up by observational data is due to a number of technical factors, including the limitations of certain research methodologies, the lack of sound immunological test methods and diagnostic shortcomings.

Regarding immunological tests, sometimes not the correct test is used or the test used is insufficient specific for the allergen in question. Sometimes no suitable tests are available at all, in particular for those allergens that induce non-IgE-mediated immune responses. In those cases first adequate tests need to be developed to detect correctly allergic sensitisation.

In the context of diagnosis, it is important to establish the cause of the illness. Respiratory disorders can have many causes – one being allergy, another being irritation. If exposure is liable to induce both allergy and irritation, it is not surprising if some studies come across people who have a respiratory condition, but are not specifically sensitised. In practice, allergy and irritation are closely related. By performing additional immunological tests, it can be assessed whether the symptoms are actually caused by an allergy.

It is also worth noting that, when calculating an occupational exposure limit, all potential adverse health effects should be considered, in order to identify the most critical effect. The exposure limit should then be geared to the prevention of the effect in question, which will necessarily entail the prevention of less sensitive effects as well.

6.3 Conclusions

Where allergic respiratory disorders are concerned, the committee is of the opinion that allergic sensitisation should be regarded as the critical effect. It is the best starting point for the calculation of toxicology-based recommended OELs, since it plays a crucial biological role and is a prerequisite for the development of allergy. Once sensitisation has occurred, continued exposure will lead to allergy in most cases.

In line with this conclusion, the focus in the remainder chapters is on response data regarding allergic sensitisation.

Chapter 7

Determination of a threshold level

As indicated in the introduction to this advisory report, occupational exposure limits are derived from toxicology-based OELs. The latter are themselves based on current scientific knowledge regarding the toxicity of the substances in question. Where non-carcinogenic substances are concerned in the occupational situation, this knowledge is used to calculate so-called health-based recommended occupational exposure limits. In principle, allergens are among the substances that can be addressed on this basis. However, the calculation of a health-based recommended OEL requires the identification of a concentration level, a threshold level, below which it may reasonably be expected that there is no risk of adverse health effects. In this chapter, the committee considers whether threshold values can be determined for allergens. To this end, the committee reviews what is known about the relevant immunological effect mechanisms, and the evidence available from epidemiological and animal studies.

7.1 The immunological mechanism of action

From a biological point of view, it is interesting to know whether a single molecule of an allergen is capable of inducing allergic sensitisation. If that is the case, no threshold level can be established: any exposure, no matter how low, entails a risk.

Present scientific knowledge regarding IgE-mediated immune responses would suggest that only a few allergen molecules are needed to evoke an

immune response: at least one, which is traced and processed by antigen-presenting cells, so that these cells are able to activate naive T cells, and at least one to co-stimulate B cells to mature into IgE-producing plasma cells.

However, considering the way that the immune system as a whole behaves in the context of hypersensitivity, the committee believes it unlikely that in reality just a few allergens are needed to provoke a specific response (whether IgE-mediated or non-IgE-mediated). The reason being that the immune system is characterised by a complex system of regulatory mechanisms, involving cells of several different types located in various parts of the body. These cells respond to each other by positive and negative feedback mechanisms. Only when appropriate feedback is no longer received – in the event of the presence of allergens in critical quantities, for instance – can an imbalance arise, resulting in an allergic immune response.

Nevertheless, the committee expects that the threshold levels for the induction of immune responses, and thus for the occurrence of allergic reactions, are likely to be very low. So low that the committee doubts whether a threshold can in practice be detected for most allergens. The way that the immune system works means that is has to be capable of responding to allergens in very small quantities. Hence, the system is 'designed' to make this possible: lymphocytes that can recognise a particular antigen are kept on standby, ready to start multiplying as soon as the relevant allergen is presented by an antigen-presenting cell and the appropriate co-stimulating factors are present.

The committee therefore concludes that, theoretically, there should be a threshold level, below which it may reasonably be expected that there is no risk of allergic sensitisation. However, this threshold is expected to be very low. One must therefore ask whether such a threshold can actually be discerned on the basis of epidemiological or animal research findings.

7.2 Observational research findings

Observational research is an important source of information concerning the health effects of inhalant allergens. However, most of the available information relates to a small number of allergens, such as flour dust, fungal alpha-amylase, proteins found in the urine of laboratory animals, diisocyanates, acid anhydrides, and soluble platinum salts. A comprehensive review of exposure-response data concerning individual and occupationally relevant inhalant allergens is presented in a survey article by Arts *et al.*[15]

7.2.1 *High molecular weight allergens*

From the body of available data, one may observe a significant and consistent rise in the prevalences of allergic sensitisation and allergic respiratory symptoms as exposure increases. Similar associations to those observed with work-related allergens have also been suggested for cat and dust mite allergens in the general population.[177,216] However, the findings of various studies also indicate that, at higher exposure levels, the risk ceases to increase and may even decrease slightly. This observation may be attributable to the healthy-worker effect, or to the development of high-dose tolerance. However, it is uncertain how relevant the occurrence of tolerance is in preventing the development of sensitisation, because the mechanism of tolerance is not entirely clarified yet, and no clear data are available concerning occupational exposure.[125,145,219]

Problems in the determination of a threshold level

To be able to assess reliable threshold levels, data are needed that define the precise nature of the relationship between exposure and response. To establish the course of such exposure-response relationships, it turns out that the available data give limited information. This hampers the assessment of threshold levels. How this comes will be considered below.

The object of most of the published studies was primarily to determine *whether* there was a positive association between exposure and allergy, rather than to define the precise nature of that relationship. Some of the studies demonstrated the existence of a positive association, by using a simple statistical model to plot a linear trace on the basis of response data for a small number of exposure levels. Such an approach may be the norm for addressing the issue with which these studies were concerned, but it is wholly inadequate as a means of acquiring detailed insight into the nature of the relationship and thus of establishing whether there is a threshold, below which no effects may be expected. A conclusion regarding the existence of a threshold depends on the availability of data relating to a variety of exposure levels and on the performance of a detailed statistical analysis to determine the form of the exposure-response relationship. These requirements imply a different research methodology. The committee suspects that some of the data necessary for investigation of the threshold question were in fact collected by the researchers, but not reported, being irrelevant to the study objectives. If reprocessed and re-analysed, these data could help to establish whether threshold levels can be determined.

Another problem derives from the intrinsic characteristics of observational research, albeit characteristics shared to some extent by experimental research. An observational study is concerned with the levels of exposure that occur in practice, as measured within a given range. If it happens that there is a clear threshold level detectable somewhere in the middle of that range, the study data are likely to be useful in its identification. If, however, a threshold threatens to fall at the extreme lower end of the observed exposure range, it will be much harder to discern from the study findings. Epidemiologically speaking, the information is more difficult to characterise, because there are typically fewer response data concerning the lower end of the range and distinction from the background incidence tends to diminish. This in turn increases the uncertainty inherent in the interpretation.

The problems are even greater if the threshold level is liable to fall outside the observed exposure range. Under such circumstances, it is necessary to estimate the form of the exposure-response relationship outside its observed extent, and to deduce the position of any threshold level from the estimated data. It is open to question – especially if uncertainty exists concerning the precise form of the exposure-response relationship within the observed exposure range – how much evidential value such estimated data have. According to Crevel *et al*. the uncertainties may (depending on the chosen elicitation effect level) be too great to permit reliable estimation.[50] The authors in question base this conclusion on the results they obtained using various statistical models in combination with food allergy data.

Al these factors make it very difficult to pinpoint the threshold level for a given inhalant allergen. In this context, it is instructive to consider the two practical examples set out below.

Example 1: fungal alpha-amylase

The available research data provide only a broad outline of the relationship between occupational exposure to fungal alpha-amylase and the occurrence of specific sensitisation. Three cross-sectional studies have been performed in the flour production and processing industry, providing both exposure and effect data.[105,120,194,209] The three studies were mutually independent and involved separate study populations, but used the same method to measure personal exposure to airborne allergens.

Notably, the levels of exposure and response measured by the three research teams were broadly similar, suggesting that all the studies were competently performed in line with modern principles. Each research population was divided

into three otherwise similar groups on the basis of the level of exposure. A positive association was observed between the average fungal alpha-amylase concentration and the prevalence of specific sensitisation (as demonstrated by skin prick testing). The prevalence data are compared in Figure 7.1. Figure 7.2 illustrates the exposure-response relationships discerned from the separate studies, in the form of a linear trace plotted on a logarithmic scale by applying semi-parametric techniques to data for a number of different measurement points.

However, neither the number of measurement points used nor the power of the analytical technique are sufficient to define the exact form of the exposure-response relationship observed in any of the three separate studies at low exposures. It appears that there was an effect even at the lowest observed exposure level, but it is not possible to be sure; certainly no clear threshold level was discernible within the observed exposure range. Furthermore, the uncertainties are too great to permit the estimation of where a threshold might lie.

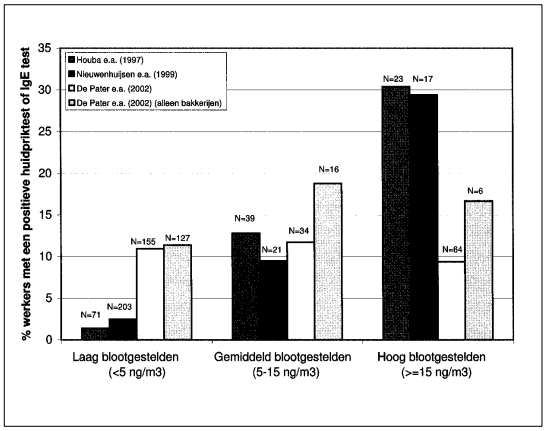

Figure 7.1 Comparison of the prevalences of specific sensitisation to fungal alpha-amylase, as observed in various cross-sectional studies (figure source: Heederik *et al*. 2004).[105] Note of translation on X-axis: bars on the left (low exposed, < 5ng/m³), mid (averaged exposed, 5-15 ng/m³), and high exposed (>= 15 ng/m³); Y-axis: % of workers with a positive SPT or IgE-test.

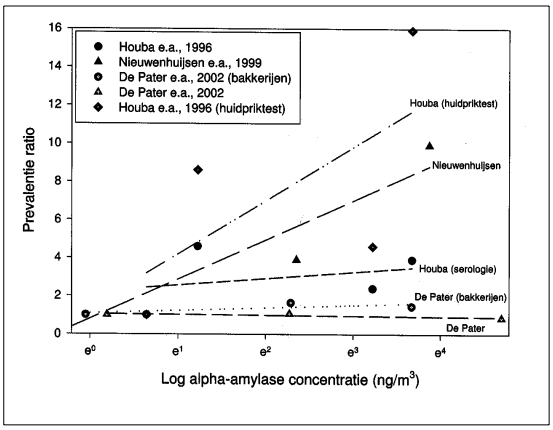

Figure 7.2 Exposure-response relationships between fungal alpha-amylase and the occurrence of specific sensitisation. The prevalence ratio relates to the prevalence of a response in the average-exposure and high-exposure groups relative to the prevalence in the low-exposure group. Data from various cross-sectional studies (figure source: Heederik *et al*. 2004).[105]

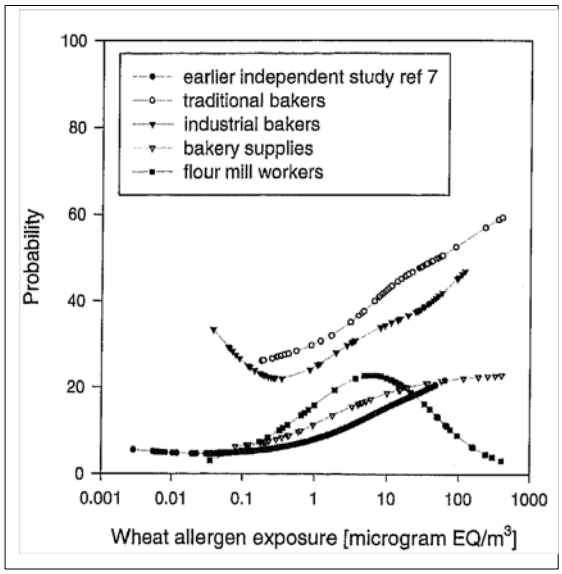

Figure 3.3 Probability of sensitisation to wheat flour dust as a function of exposure to the inhalable agent, as ascertained from actual wheat allergen measurements (mEQ/m³), in each of several industries plotted on a log scale; the relationship reported in an earlier independent study (ref 7) is also shown. Source: a cross-sectional study by Peretz *et al.* (2005).[213]

Example 2: wheat and other cereal flour dusts

A good survey has been performed on the relationship between exposure to wheat and other cereal flour dusts and a specific sensitisation response. The information comes from two mutually independent Dutch cross-sectional studies, by Heederik *et al.* and by Peretz *et al.*[107,213]

The study by Peretz *et al.* looked at various industries in which exposure to flour dust was commonplace.[213] The average concentration of airborne wheat allergens to which each worker in the study was exposed was predicted using a statistical model, on the basis of the industry in which the individual worked and his or her role and duties. Then the form of the association between the predicted exposure and the occurrence of specific sensitisation was analysed using a semi-parametric additive model; the results thus obtained are presented in Figure 3.3. The figure also illustrates the findings obtained by Heederik *et al.* (the 'earlier independent study ref 7').[107]

From the results, it is apparent that the probability of sensitisation to wheat flour dust increases with increasing exposure and that there is a risk of sensitisa-

tion even at the lowest observed level of exposure. It is not therefore possible to determine a threshold level from these data.

Conclusion

In the first example, the committee concludes that data are insufficient to determine a reliable threshold level. More research is needed to get the needed information. In the second example, sufficient data are collected, but still no clear threshold level was observed. It is not expected that the missing data are soon available, because of technical shortcomings. Data on other allergens with a high molecular weight, such as those found in the animal care sector, and bell pepper and flower horticulture, are even scarcer, and thus difficult to interpret.

7.2.2 Low molecular weight allergens

Interpretation of the data available concerning LMW allergens proves for some of these allergens to be even more difficult than interpretation of those concerning HMW allergens, because the immunological mechanism that gives rise to the allergic phenomena is only partially understood and there is no reliable way of testing for non-IgE-mediated sensitisation. Furthermore, interpretation of allergic respiratory disorders is complicated by the fact that most LMW allergens also possess irritant properties.

Various epidemiological and animal studies indicate that the prevalence of allergic sensitisation to acid anhydrides, diisocyanates and platinum salts, and of associated respiratory disorders and bronchial hyperresponsiveness, increases with exposure.

In a Swedish prospective study, for example, a group of previously unexposed workers (n=163) was monitored over an average period of two and a half years for the occurrence of specific sensitisation to organic acid anhydrides.[273] New cases of sensitisation occurred during the observation period even in the lowest-exposure group (exposure: 0-5 µg/m^3). A similar finding was made in a cross-sectional study of the same study group, while no cases of specific sensitisation were encountered in a non-exposed group.[192]

With regard to toluene diisocyanate (TDI), no cases of specific sensitisation (tolyl-reactive IgE antibodies) were found in a group of new workers (n=103) who were exposed to 0.02 ppm TDI (≈0.16 mg/m^3) or less over a period of three years; raised levels of the antibody were found in the blood of workers who experienced accidental acute exposure to TDI, however.[135] No exposure-response relationship could be deduced from this data set. Exposure-response data

obtained from a study of a group of spray painters, who were exposed to hexamethylene diisocyanate oligomers, showed a positive association between the increase in exposure and specific IgG-mediated sensitisation.[222] The number of IgE-sensitised workers was very low, suggesting that IgE-mediated immune responses play a minor role in the development of diisocyanate oligomer-induced allergies.

Merget *et al*. performed a prospective cohort study of a group of workers who were exposed to soluble platinum salts on a daily basis.[172,174] A little over half of the workers were already employed in the relevant industry at the start of the study, while the others were newcomers. Analysis of the findings indicated that no new cases of specific sensitisation (as determined by skin prick testing) occurred among workers exposed to less than 10 ng/m^3 during a five-year follow-up period. At the moment of publication of this advisory report, DECOS, a committee of the Health Council, evaluates this study. DECOS tentatively concluded that the study of Merget *et al*. is valid and of sufficient quality, as such that a threshold level can be determined on allergic sensitisation.[92]

Conclusion

It seems that human data on a few allergens with a low molecular weight are sufficient to derive a threshold level. However, in general, human data on exposure-response relationships are scarce, and this includes those of high molecular weight allergens. As a consequence, for these allergens it is difficult to determine the height of the threshold level.

7.3 Animal research findings

The significance of animal research

Animal research can contribute to the evaluation of substance toxicity, because the use of animal models facilitates data collection, and because the exposure conditions in such research are controlled.

Various animal species are used in allergy research, such as mice, guinea pigs, rats and sometimes dogs. Furthermore, in the majority of the animal models biphasic protocols are used; in a first exposure phase allergic sensitisation is initiated (initiation phase), then, after a short rest period, there follows a second exposure phase to induce elicitation (challenge phase). Sensitisation can be induced by different routes, such as via the skin, intraperitoneal injections, inhalation and introduction to the nose or trachea. During the second phase, exposure

to the same allergen takes place via the skin, lungs (inhalation), or nasal epithelium. The route and level of exposure can differ between the two phases. Exposure is almost always single-instance or repeated within a short period. In some cases, sensitisation is measured directly after the initiation phase (by reference to specific antibodies in the blood). Usually, however, the measured indicators are post-challenge reactions (breathing frequency, breathing pattern, non-specific bronchial provocation reactions, lung pathology).

Researchers seek to imitate the human situation, including exposure conditions, as far as possible when developing animal models for allergy research; nevertheless, this tends to prove very difficult in practice. One reason can be that the laboratory animal species used does not naturally develop the condition that the researchers are interested in. Mice, for example, do not naturally develop allergic rhinitis or asthma.[112] Furthermore, many animal models involve dermal exposure, whereas it is exposure by inhalation that is relevant in the context of occupational exposure limits. In addition, most protocols are designed to determine allergenic potency, rather than to identify threshold levels. Consequently, exposure is generally of short duration. As a result, no animal inhalation models or test protocols are generally accepted or used for risk analysis at present.[13] New animal models are under development, such as the local lymph node assay (particularly for research into inhalation allergies), but it is too early to say whether the results will be suitable for risk analysis.[13,210,212,266]

The factors outlined above make it difficult to define recommended OELs for allergens on the basis of data on allergic sensitisation obtained from animal research. Nevertheless, animal models can contribute significantly to our understanding of allergy and can support epidemiological research findings. The animal research findings that shed light on the question of whether it is possible to identify threshold levels for sensitisation are accordingly summarised below. The reader is additionally referred to the publication by Arts *et al*. (2006).[15]

Findings concerning allergens with a high molecular weight

Few animal studies have focused on the induction of allergic sensitisation by the inhalation of allergens with a high molecular weight. Some data have nevertheless been published on enzymes, such as alcalase and subtilisin, and the protein ovalbumin. These data come from (monophasic) studies, in which guinea pigs or rats were exposed to various concentrations for short periods of time. Although allergic sensitisation was found to increase as exposure increased, none of the studies yielded evidence of a threshold level.[15,266]

Findings concerning allergens with a low molecular weight

A larger number of animal studies have investigated the effects of allergens with a low molecular weight, in particular acid anhydrides and diisocyanates.

For instance, Sarlo *et al*. exposed a small group of guinea pigs to various concentrations of phthalic acid anhydrides.[237,266] Before initiation and before the challenge, blood samples from the animals were tested for specific IgE and IgG_1 against the conjugate of phthalic acid anhydride-guinea pig albumin. No specific IgE was found in any of the animals. However, clear rises in both specific IgG_1 and total IgG were observed as exposure increased. Even at the lowest exposure level, the levels of IgG were found to be raised. However, no threshold was observed.

In other studies, trimellitic acid anhydride has been investigated using rats and mice.[11,14,33,281] In the studies concerned, sensitisation was initiated by dermal exposure, followed by inhalatory exposure in the challenge phase. In these studies, no data were collected on the induction of allergic sensitisation directly after initiation and immediately prior to challenge. Furthermore, because the study designs involved initial dermal exposure, it is almost impossible to draw any conclusions regarding the existence of a threshold for inhalatory exposure. Apart from that, in a number of the studies, a threshold was observed for changes in lung function after the challenge.[11,281]

Data have also been published on diisocyanates, including toluene diisocyanate (TDI), diphenyl methane-4,4'-diisocyanate (MDI), dicyclohexylmethane-4,4'-diisocyanate (HMDI) and 1,6-hexamethylene diisocyanate (HDI). Regarding TDI, allergic sensitisation was observed in a (monophasic) study involving guinea pigs. The relationship was found to be log-linear; in the lowest-exposure group (exposure: 0.12 ppm (≈ 0.96 mg/m^3)), no antibodies were found seventeen days after the final exposure and the results of a bronchial provocation test using TDI protein were negative.[136] Positive results were obtained, though, in tests on animals exposed to 0.36 ppm or more.

Pauluhn *et al*. described a biphasic study on homopolymers and monomers of HDI.[211] During initiation, guinea pigs were exposed to various concentrations of HDI by inhalation. The challenge involved the most reactive HDI-protein conjugates, with inhalation again the mechanism of exposure. Before the challenge, measurements showed an increase in anti-IgG_1 levels in the blood at increasing exposure; in non-exposed animals, and in animals exposed to the lowest concentration of homopolymers, no increased levels were found.

In a biphasic study by Stadler *et al*., guinea pigs and mice inhaled various concentrations of HMDI.[247] The challenge involved dermal exposure and the

effect parameter used was the degree of redness of the skin (erythema). In both species, redness was found, of which the degree increased as exposure increased. No skin effects were found at the lowest exposure level or in non-exposed animals.

In a study of the monomer MDI, Rattray *et al*. did not find elevated levels of specific IgG_1 in the blood of guinea pigs after inhalatory exposure.[223] In the same study, however, elevated levels were found after dermal exposure.

Conclusion

Animal data on certain low molecular weight allergens show no measurable effects at low levels of exposure. However, the data should be interpreted cautiously, because the study designs were complex in some cases, the exposure periods were relatively short, and numbers of animals used were small.

7.4 Conclusions

On the basis of scientific knowledge and understanding of the relevant immunological effect mechanisms, the committee concludes that there should be a threshold level, below which allergic sensitisation to any given allergen does not occur. However, this threshold level is likely to be very low in most cases.

Where a few allergens are concerned, the committee considered whether a threshold level could be deduced from epidemiological data. It was concluded that this appeared to be possible in the case of soluble platinum salts. However, for (wheat) flour dust allergens, no threshold level was observed, even at low exposures. Further research is needed before conclusions may be drawn regarding other allergens.

Threshold levels were observed in a few animal studies, but not in others. The committee would emphasise, however, that animal research findings need to be interpreted cautiously, because experimental exposure conditions differ significantly from the exposure conditions in the workplace and because there is no animal inhalation model available that has been validated and is accepted for risk analysis.

Chapter 8

The calculation of recommended OELs

Recommended occupational exposure limits on the occupational setting are calculated in accordance with a procedure and using methods, which have been described and discussed in detail in the scientific literature. Thus, where non-carcinogenic substances are concerned, health-based recommended occupational exposure limits are calculated. Such a limit is an expression of the level of exposure to an airborne substance, at or below which it may reasonably be expected that there is no risk of adverse health effects. As indicated in the previous chapter, scientific knowledge of the immunological effect mechanisms involved in allergy points towards the existence of such a threshold exposure level for allergic sensitisation. Hence, the current procedure requires that one should first consider whether a health-based occupational exposure limit can be calculated.

8.1 Methods used to calculate health-based recommended OELs

Health-based OELs are defined in a prescribed sequence of steps and in accordance with fixed decision-making rules. Since these are described in detail in other Health Council reports, this report provides only a brief summary.[84-86]

Assuming that it has been adequately ascertained that an inhaled substance causes allergic sensitisation and respiratory allergy, and assuming that allergy is considered the critical effect, the next step is to collect and evaluate data on exposure and response. These data are then used to establish a health-based OEL.

In the Netherlands and elsewhere, the most common way of calculating a health-based OEL is to determine the highest exposure level which does not lead to adverse health effects. This is the so-called no-observed-adverse-effect-level or NOAEL. This level should preferably be calculated from epidemiological data, but use may also be made of data from experiments on human volunteers or animals. An 'uncertainty factor' is then applied to allow for the differences between laboratory animals and humans, differences in sensitivity between individual humans, and research data deficiencies. The exposure level thus calculated is adopted as a health-based recommended occupational exposure limit.

The NOAEL method has certain shortcomings, the most important of which is that an NOAEL value depends significantly on the quality of the available research data. The less precise the data are, the higher the corresponding NOAEL value is likely to be. An alternative approach, which entails less inherent uncertainty, has therefore been developed: the benchmark dose method (BMD method).[86] The BMD method seeks to analyse the data on the effects of a chemical in order to determine, as accurately as possible, the relationship between a given exposure level and the likelihood of its detrimental effects (the so-called response). The statistical uncertainty to which these data are invariably subject is incorporated into the calculations. The figures are then used to yield a 'benchmark dose' or BMD; this is the dose which corresponds with a given value, for instance 1 per cent or 10 per cent. The BMD is then divided by an uncertainty factor to yield a health-based recommended occupational exposure limit.

Application of the benchmark dose method involves making certain decisions. For instance, a decision needs to be made regarding the point at which an effect may be deemed not to constitute health impairment; furthermore, it is necessary to define a model function to describe the form of the exposure-response relationship.

For the calculation of health-based recommended OELs, the Health-Council prefers the BMD method over the NOAEL method.[86] It is apparent, however, that current toxicity research protocols do not facilitate the use of this method. In consequence, the method is not yet widely used, certainly in connection with epidemiological data. However, statistical methods exist for the analysis of epidemiological data, whose potential is similar to that of the BMD method.

8.2 Problems associated with health-based recommended OELs

Regardless of the calculation method used, a health-based recommended OEL is most reliable if, within a given exposure range, a clear threshold is discernible, above which an adverse health effect is observable and below which no adverse

health effect is observable. When that is not the case, a threshold can be estimated by extrapolation methods. However, this introduces uncertainties, for which correction is required. In some cases, these uncertainties may be so great that no reliable health-based recommended OEL can be calculated. Under such circumstances, it is necessary to obtain response data for the lowest exposure levels by means of additional research before progress can be made.

Sometimes, however, data on very low levels of exposure are not obtainable because of the limitations of existing research methods, and it is unlikely that more sophisticated techniques will become available in the near future. In view of the immunological effect mechanisms involved in allergy, which suggest very low threshold levels, and considering the available epidemiological and animal research data, the committee assumes that the latter situation is likely to exist where many allergens are concerned.

This implies that it is not currently possible to calculate reliable health-based recommended OELs for such allergens, even though ample data regarding higher levels of exposure are available in some cases. The non-use of such valuable data strikes the committee as regrettable in view of the health problems experienced by workers as a result of exposure to allergens. Since the committee considers it important that workers are protected, it has explored the possibility of using an alternative approach in order to calculate recommended OELs for such allergens.

For those substances concerning which no data are available regarding either lower or higher levels of exposure, the committee suggests that standards should for the time being be based on the manifestation of allergic respiratory symptoms. The committee emphasises, however, that from a health perspective this is not ideal.

8.3 Reference values as an alternative approach

There is a group of carcinogens, which are believed to constitute a health risk at any level of exposure. For this group an alternative approach is developed. The product of this are reference values corresponding to risks of cancer mortality.[84,93] These reference values provide a basis for the assessment of an occupational exposure limit. The committee has considered whether this approach could also be used for allergens, in cases where no reliable health-based recommended OEL can be calculated, but where there are in principle ample exposure and response data available.

The approach involves determining the lowest exposure level at which adverse health effects are observed. By means of linear extrapolation, exposure values are then calculated which correspond to predefined extra levels of

response risk. Such exposure levels can also be calculated using the benchmark dose method. The exposure values or reference values thus calculated provide a basis for the assessment of an occupational exposure limit.

For carcinogens reference values are calculated corresponding to the likelihood of an extra four cases of cancer mortality – as a result of working life exposure – in relation to the number of cases of cancer death per 1,000 and per 100,000 death cases in the general population. Thus, the method defines levels of exposure that are deemed to entail unacceptable added risk and negligible added risk, respectively. The additional risk of cancer mortality due to carcinogen exposure is generally accepted in the Netherlands, and these levels of risk are widely employed for regulatory purposes.

The accepted risk levels referred to above are applied only in relation to cancer mortality. Their inclusion in this advisory report is purely illustrative. The reference-value approach would require adaptation for use in relation to the appearance of allergic respiratory sensitisation. The acceptability of a given level of risk of allergic sensitisation depends not only on health-related considerations, but also on policy and social considerations. Considerations of the latter kinds are outside the remit of the committee, which has accordingly confined itself below to examining the relevant health-related considerations.

The added risk of cancer mortality is expressed in absolute terms. However, it may be more useful to express the added risk of allergic sensitisation in relative terms, *i.e.* as the increase in risk relative to that associated with the background prevalence of the allergen in question. The logic behind such an approach is that background prevalences differ from one allergen to the next, and that the background risk of sensitisation in the general population will therefore also differ from one allergen to the next. Defining added risk in relative terms will not be easy, however, because background prevalences depend not only on exposure, but also on other factors, such as how widespread exposure to the allergen is in the general population, the type of allergen and personal factors, such as age. Hence, thorough research into the reliability of background prevalence values would be required.

Alternatively, limits might be defined using an approach based on disease burden. Disease burden may be quantified in terms of QALYs or DALYs (see section 5.4). Hence, one may seek to limit disease burden to a certain level, for which a corresponding exposure level could be calculated. At present, however, there are almost no data on disease burden for sensitisation or allergic respiratory disorders in the general or occupational population. In view of these considerations, judgements regarding the feasibility and practicability of using such an approach for occupational health and safety regulation must be deferred.

8.4 Findings and directive regulations from other countries

What follows is a summary of the main countries and organisations that have drawn up guidelines and evaluate the toxicity of substances used in the workplace. Also attention is paid to the European regulations regarding sensitising substances.

Exposure limits

The European Scientific Committee on Occupational Exposure Limits (SCOEL), whose task is to advise on occupational exposure limits at the European level, uses the following methodology: 'If the data concerning a substance provide sufficient evidence that there is a threshold level for sensitisation, the SCOEL can recommend a health-based occupational exposure limit in accordance with the principles set out elsewhere in this publication. If it is unclear whether such a threshold exists, the SCOEL takes the view that no health-based occupational exposure limit can be determined and confines itself to advising the Commission regarding the risk of sensitisation of the respiratory tract associated with certain exposure levels (in a similar manner to that defined for genotoxic carcinogens)'.[72] At the moment the SCOEL prepares an evaluation document on (wheat)flour dust. In this document it is written that for sensitisation no threshold level can be derived, and that it is therefore better to base a recommended exposure limit on airway complaints. What will be the final proposal for an occupational exposure limit is not known yet.

The UK's Health and Safety Executive (HSE) has indicated that threshold levels cannot be calculated for allergens.[103] If exposure cannot be avoided, the HSE recommends setting an occupational exposure limit as low as practicable.* Where asthmagenic substances are concerned, the appearance of symptoms serves as the point of reference for the calculation of occupational exposure limits, regardless of the mechanism of the illness. Using this approach, the Maximum Exposure Limit for (wheat)flour dust was set at 10 mg/m^3.[193]

In Germany, the *Deutsche Forschungsgemeinschaft* (DFG) also takes the view that threshold levels cannot be calculated for allergens, and indicates that the risk of induction increases with increasing exposure.[63] It has additionally stated that, even if an occupational exposure limit is calculated for an allergen,

* The British ALAP principle corresponds with the ALARA principle (as low as reasonably achievable) of the legislation and regulation in the Dutch governments' environment and health and safety at work policy.

the possibility cannot be excluded that sensitisation will occur and allergic respiratory disorders will develop.

In Sweden and Denmark, occupational exposure limits are calculated for inhalant allergens in the same way as for other agents.[8,9] This means that threshold levels are used to establish exposure limits for allergens. In Spain on the other hand the approach by SCOEL is followed.

Outside Europe, the American Conference of Governmental Industrial Hygienists and the National Institute for Occupational Safety and Health derive exposure limits for inhalant allergens in the same way as for other agents.[6,179]

Sensitisation assignments

Different criteria are used around the world for the assignment of letters (S, SEN) to sensitising substances.[6,8,63,103] Such an assignment is a warning for employers and employees to take measures to prevent sensitisation of an allergen. In the Netherlands such an assignment does not exist. In countries different criteria are used for the sensitisation assignment. In some countries, for example, the coded agents include those which cause sensitisation by a non-immunological mechanism; sometimes, no distinction is made between skin, eye and respiratory sensitising agents. Therefore, it is not always clear whether sensitising substances can induce allergies.

The World Health Organization has gone a step further by proposing the division of respiratory sensitising agents into four classes: I (inducer of specific airway hypersensitivity) to IV (not an inducer of specific airway hypersensitivity).[279] To the best of the Health Council's knowledge, this proposal has not yet been adopted by any country.

Labelling

Finally, European Union regulations include directives to warn users for the hazards of chemical and biological agents. One of the directives includes putting a warning sentence on the package of agents that are considered toxic for humans.

For agents that cause sensitisation through inhalation the symbol R42 should be used: may cause sensitisation through inhalation. However, according to the definitions used in those directives, natural products and raw materials, such as grains, plant products, wood and animal products, do not fall under this rule, and thus no warning sentence is needed. This is a problem, since in certain industries, such as bakeries and horticulture, mainly natural products are used and the prevalence of occupational respiratory allergy is large. In other cases, warnings are

put on packages for the whole product containing a mixture of agents, such as enzymes, but further specification on which agent in the products cause sensitisation is not needed.

In 2007, a new European chemicals regulation went into practice to manage chemical products (REACH). However, substances that are natural of origin and of which the chemical composition is not changed, including foodstuffs, do not need to be registered. This means that part of the allergic agents of natural origin do not fall under this regulation.

8.5 Conclusions

The committee concludes that health-based occupational exposure limits can be calculated for inhalant allergens using the same procedures and methods as those used for other non-carcinogenic substances. Hence, the first step towards calculating such a limit is to determine whether, in the given instance, it is possible to use a method such as the common no-observed-adverse-effect-level method, the benchmark dose method, or another similar statistical model for human data.

However, the committee believes that, where most allergens are concerned, it will not be possible to calculate a reliable health-based occupational exposure limit by any such method. For scientific knowledge of the immunological effect mechanisms involved in allergy suggests that, in most cases, the threshold level will be too low to discern using the techniques presently available. The committee regards the difficulty of calculating reliable health-based occupational exposure limits as a matter of concern, since allergies are a significant problem, against which workers should be protected. The committee has therefore explored the possibility of using an alternative approach for those allergens for which reliable health-based OELs cannot be calculated. This approach involves determining reference values, or concentration levels, which correspond to predefined accepted levels of risk of allergic sensitisation. These reference values can then be used as a basis for the assessment of occupational exposure limits. The committee recommends that the predefined accepted level of risk should take account of the background prevalence of the allergen in question. However, the final decision on the predefined accepted level of risk will also depend on policy and social considerations.

Chapter 9

Periodic screening

In practice it should be taken into account that a worker who is exposed to inhalant–allergens may become sensitised and, if exposure continues, may develop an allergy.

To protect people for the adverse health effects of exposure to allergens a regulation exists that dictates that in the first place workplace exposure should be reduced. If that is insufficient, other measures are necessary. One of the possibilities that are considered by the minister is the introduction of periodic screening. This matter is addressed in this chapter. Paramount is the question whether periodic screening on allergic sensitisation is a meaningful premise and feasible to prevent the development of allergic symptoms.

9.1 Screening as a means of prevention

Basically, to prevent health problems in humans or to prevent worsening of the existing problems there are three strategies. The first strategy is to prevent new illness cases by removing the cause of illness (primary prevention). The second strategy entails the detection of illness at an asymptomatic stage, so that treatment may be provided and progression prevented (secondary prevention). And finally, the last strategy is any form of prevention whose purpose is to improve the condition of a person who has already contracted an illness and to reduce the associated disease burden (tertiary prevention).

In an occupational context, (periodic) screening is a form of secondary prevention. Where inhalant allergies are concerned, the best approach appears to be to seek to identify workers who have become sensitised but have yet to develop symptoms, or whose symptoms are as yet mild.

Periodic screening can also yield information that is of used in setting up monitoring programmes. These programs are meant to identify trends within a company or an industrial sector, and eventually to take measures which are beneficial for the health of workers.

A screening programme can also serve as a vehicle for tertiary prevention, that is when (allergic) respiratory disorders are already present. Tertiary prevention is a valuable tool if there are no means to perform primary and secondary prevention, and if the prevalence of respiratory complaints due to exposure to allergens is relatively high. In this report, however, the main focus is on secondary prevention.

Screening has ethical and socio-political dimensions, since it touches on the right to information, withholding information, intervention, personal autonomy, stigmatisation and psychical discomfort – which are not matters of (scientific) fact, but have a significant bearing on acceptance to persons who it concern. These matters have been thoroughly examined by other bodies, leading, for example, to a consensus that no one may be obliged to submit to screening.[184] Regarding the tasks and competence of the committee, in this report no further consideration of such ethical matters is given. The committee thus confines itself largely to the desirability and effectiveness of periodic screening as a means of protecting workers against the harmful effects of inhalant allergens.

9.2 Screening appraisal criteria

Periodic screening is of value only if it has the potential to provide a significant health benefit, and this benefit justifies the efforts and costs that are associated by introducing a screening programme. To gain insight into these factors, in the 1960s, at the request of the World Health Organisation, Wilson and Jungner defined ten criteria for appraising the validity of a screening programme for the general population:[240,276]

1 The condition sought should be an important health problem;
2 Treatment started at an early stage should be of more benefit than treatment started later;
3 Facilities for diagnosis and treatment should be available;
4 There should be a latent or early symptomatic stage;
5 There should be a suitable and acceptable screening test or examination;

6 The test should be acceptable for patients with the disease;
7 The natural history of the disease should be adequately understood;
8 There should be an agreed policy on whom to treat as patients;
9 The cost should be economically balanced in relation to possible expenditure on medical care as a whole;
10 Case finding should be a continuing process and not a once and for all project.

These criteria still form the basis for the decisions on screening programmes in the Netherlands, albeit often adapted or supplemented to suit the specific circumstances. Reworded versions of some of the Wilson-Jungner criteria have been incorporated, for example, into the Netherlands Society for Occupational Medicine's (NVAB) guidelines on the performance of preventive medical examinations in the occupational health care sector.[184] In addition, in the Netherlands are defined a number of guiding principles, which are intended primarily to ensure good implementation and information provision:[240]

- The intervals between testing and result availability and between result availability and treatment must be kept as short as possible.
- The call-up system must not infringe the individual's freedom to decide whether or not to participate in the screening programme.
- Potential participants must be properly informed about the advantages and disadvantages of participation.
- Public information activities must promote the general accessibility of the programme, but must not exert moral pressure.

In the process of reviewing, the Wilson-Jungner criteria should be viewed in conjunction, rather than as a list of conditions which must all be fulfilled.[91] In other words, a screening programme may be desirable, even if not all the criteria are met. However, the non-satisfaction of one or more criteria should be offset by comfortable satisfaction of the others.

9.3 Appraisal against the criteria

The committee subscribes the criteria of Wilson and Jungner. To judge whether periodic screening on allergic sensitisation is a meaningful premise and feasible to prevent the development of an occupational inhalation allergy, the committee has examined whether the key criteria by Wilson and Jungner and their followers are fulfilled. The most important findings on the early tracing of sensitised persons are presented below.

9.3.1 *The condition sought should be an important health problem*

The NVAB words its corresponding advice as follows: 'The seriousness and consequences of the adverse health effect(s) that the programme is intended to prevent (work disability, incapacitating nature, inconvenience, cost) must be significant.'[184]

Allergic sensitisation is not in itself a health complaint. However, sensitisation is a condition, which can lead to serious and irreversible health problems, such as allergic asthma and allergic rhinitis. Such disorders have a negative effect not only on individual quality of life (*e.g.* physical and mental discomfort), but also on socio-economic status (*e.g.* through absenteeism, diminished career prospects and inability to work). It also affects disease burden.

Although the fact that an illness is very prevalent does not necessarily mean that it constitutes a serious health problem, the NVAB indicates that the prevalence of a condition and its predictors (risk factors) must be reasonably high in order to justify screening for it within the occupational healthcare system, because screening is less cost-effective if the chance on the disease is low.[184]

From the figures presented in chapter 5 of this report, it is apparent that a substantial proportion of exposed workers suffer problems as a result of allergic sensitisation. These include people working in the baking and flour-processing industries, laboratory animal care, and the bell pepper and flower greenhouse cultivation industry, as well as people who are exposed to natural latex, industrial enzymes, soluble platinum salts, isocyanates or acid anhydrides at work. Less is known about the prevalences of sensitisation to other work-related allergens.

Observations show that when exposure is continued after becoming sensitised, the number of workers who develop allergic respiratory symptoms may amount to several dozen percentage points (see Table 2.1). It is well possible that the presented percentages in the table would have been higher if the observation periods of the studies were longer. The committee, therefore, assumes for safety reasons that with continued exposure almost every worker, who is sensitised, is likely to develop an allergic respiratory disorder.

All things considered, the committee takes the view that allergic respiratory disorders constitute an important health problem, which is prevalent in certain industries.

9.3.2 *Treatment started at an early stage should be of more benefit than treatment started later*

Screening is of value only if arrangements are in place for treatment or assistance to prevent further progression and to mitigate or resolve existing problems following detection of the condition in the stage with which screening is concerned.[184]

Allergic sensitisation. From experimental research, it appears that well-established allergic sensitisation can cease to be detectable using the immunological test methods currently available.[97,150,203] This point is illustrated by the small case-control study performed by Merget *et al*. (2001), in which fourteen workers who were exposed to soluble platinum salts were monitored over a five-year period by means of annual screening.[173] If an individual tested positive for the relevant allergens in a skin prick test (SPT), he or she was removed from the sources of exposure. Among workers who thus experienced no further exposure, the SPT response subsequently diminished or disappeared altogether. Although most of workers in this group had work-related respiratory disorders, there appeared to be no change in lung function or bronchial response to histamine. Although this study did not involve intervention and did not include a good control group, the researchers suggested that periodic screening for specific sensitisation could be effective as a means of preventing work-related asthma.

Airway complaints. Observational research indicates that, if detected early, the problems will usually disappear or reduce as soon as exposure is ended, but that problems are liable to persist – even if exposure ends – once established for a significant period.[5,19,47,49,56,108,146,168,186,198,202,202,203,215,252,265] Although not examined thoroughly, there is a higher chance of the disappearance of the complaints when the diagnosis is made as early as possible, on a moment the complaints are yet not serious, and if further exposure is ended.[146,188,215]

Possibilities for treatment. Even if sensitisation ceases to be detectable in a test following the adoption of protective measures or the cessation of exposure, a person may experience hypersensitivity for the rest of his or her life. There is presently no means of ‘curing’ hypersensitivity. Progress is being made in the field of immunotherapy, but regarding allergies that are specifically met in the working environment; the relevant techniques remain in their infancy. It is not well investigated, for example, whether hypersensitivity can return once treatment ceases. For the time being treatment is limited to prevent symptoms.

Possibilities for intervention. For the time being the committee considers it best and most practical to monitor the health status of sensitised individuals on

an individual basis and to intervene in the event of deterioration. The moment the health situation deteriorates, immediate measures should be taken, for instance by using occupational hygienistic strategies. Depending on the seriousness of the problems, the measures mentioned in these strategies may vary from: removing or reducing the sources that cause the health problems; using engineering controls to minimize exposures (installing extraction systems); giving good advice on the risks and what to do to prevent sensitisation; and, introducing personal protective measures (*e.g.* wearing gloves or a mask). In some cases measures will be drastic, such as removal of the individual from the workplace, with the risk of losing the job. The latter is considered by the committee as the ultimate consequence that can only be considered when other possibilities do no have an effect. The committee concludes that the early detection of work-related allergic sensitisation by means of periodic screening can have a positive influence on prognosis, if linked to proper follow-up measures.

9.3.3 There should be a latent or early symptomatic stage

Allergic airway disorders arise because at first exposure a worker becomes sensitised to an allergen to which he or she is exposed (see chapter 2). Allergic sensitisation is a recognisable latent phase, which can be detected by immunological testing. During this phase, the patient should in theory suffer no health problems, but some people do experience mild symptoms of inhalant allergy. Clear complaints, such as rhinitis, rhinoconjunctivitis and asthma, do occur at renewed exposure.

9.3.4 There should be a suitable and acceptable screening test or examination

The normal methods for detecting specific sensitisation to a particular inhalant allergen are skin prick testing and serological testing. However, the committee foresees problems for a number of allergens.

In the first place, screening tests are feasible only if it is clear which immunological mechanism of action plays the principle role. Where some allergens are concerned, particularly LMW allergens, the IgE-mediated immunological mechanism is of lesser importance, making IgE-based testing inappropriate. This is problematic, since in many cases the underlying immunological mechanism is not properly understood, so that it is not clear what a test should be designed to detect. Furthermore, there is a paucity of good immunological screening tests for the detection of non-IgE-mediated sensitisation.

In the second and third place, it is also important that the available immunological tests are valid and standardised. Valid in that the test is sufficiently sensitive and specific. Low specificity will result in numerous false positive results, leading to unnecessary worry or unnecessary intervention. Low sensitivity is associated with a high rate of false negative results: people being regarded as healthy when in they are sensitised. Validity depends on various factors, including the quality of the allergen extracts and the standardisation of the tests. Standardised tests exist for a number of common allergens, of which stable extracts are available.[128,129,183] However, other work-related allergens have to be sampled on site, because no good quality stable extracts are commercially available. Because exposure conditions vary from one workplace to another and even one procedure to another, extracts produced from locally collected samples are liable to vary in composition, purity and thus allergenic potency. This compromises the validity of the associated tests and makes cross-workplace comparison difficult. For a number of common and widely discussed allergens, such as those originating from wheat flour, latex and laboratory animals, valid and standardised tests are available.

On a practical level, there are no obstacles to the establishment of periodic screening based on either skin prick testing or serological testing. Both types of test could be provided within the occupational healthcare sector without difficulty: they are both quick and easy to perform and the skin prick test provides an almost instant result. Furthermore, neither is generally regarded as unpleasant for the subject by ethical review bodies or the like.

The committee therefore concludes that suitable screening and validated tests are available for a number of the better-known work-related allergens. Nearly all the suitable tests are for the detection of IgE-mediated sensitisation. However, reliable and valid tests have yet to be developed (or yet to become available to the occupational healthcare sector) for many less common allergens and allergens that cause sensitisation by a mechanism in which IgE-mediation plays little or no role.

9.3.5 *The test should be acceptable for patients with the disease*

In other wording than has been done by Wilson and Jungner, the NVAB has indicated in its guidelines that neither the screening test itself nor any treatment or intervention leading from it should entail unacceptable health risks.[184] To the best of the committee's knowledge, none of the immunological tests that might be used to screen for allergic sensitisation involve unacceptable health risks. Nor are any such risks associated with the curtailment or cessation of exposure through

removal from the source or the use of personal protective measures. New health risks could arise if an allergen were replaced by another agent; the acceptability of substitution should therefore be assessed on a case-by-case basis.

Satisfaction of this criterion also depends on the acceptability of any treatment or intervention that might be indicated for a worker who tested positive. The NVAB has devised a separate criterion covering this aspect.[184] Whether intervention is acceptable to a worker depends on the likelihood that he or she will actually develop an allergic respiratory condition if exposure continues and on the nature and consequences of the particular intervention.

As indicated above, there is at the group level a very high probability that sensitisation will be followed by the development of an allergic respiratory condition in the event of continued exposure. However, it is hardly possible to predict with confidence whether a given individual will actually develop problems.

Although the committee presumes that the measures introduced in the workplace will not yield many problems, some of the outcomes are likely to be seriously problematic for the person in question. The consequences of such a person being offered comparable alternative work with similar career prospects are likely to be acceptable. However, when a person loses his or her job because neither effective exposure prevention measures nor alternative work are available – the consequences are likely not acceptable and the person might decline to participate in screening.

A precondition for the acceptability of a screening test is that subjects are properly informed about the consequences of a positive result. If consequences are considered negative, than a workers' preparedness to participate and also the way they are likely to answer question will be influenced. This was demonstrated in a comparative study by Brant *et al.* (2005).[36] In the study, the number of allergic asthma cases detected in bakery workers through routine surveillance was compared with the number detected through cross-sectional research involving the same occupational population. On average, the routine surveillance revealed only a quarter of the number of cases of baker's asthma (characterised by the presence of IgE specific to flour dust and/or alpha amylase) detected by cross-sectional research. One of the factors put forward by the researchers as a possible explanation for this striking discrepancy was possible uncertainty amongst the workers concerning the confidentiality and consequences of the surveillance. The cross-sectional research was totally anonymised and confidential, and performed by an independent study group.

The committee takes the view that the available immunological screening tests are acceptable to the target group. More difficult are the consequences that

follow after sensitisation is assessed, and the ultimate consequence is the risk of losing the job. This necessitates that subjects are properly informed about the consequences, so that they know how to judge the chance on drastic outcome.

9.3.6 *The natural history of the disease should be adequately understood*

A sensitised individual does not necessarily exhibit symptoms indicative of allergy. Such symptoms may develop, however, in response to continued exposure. Once a person has acquired an allergic respiratory condition, continued exposure is liable to aggravate it with the result that the condition ultimately becomes permanent if exposure is continued.[108,186,201] Also, more types of complaints can develop. For instance, people who initially 'merely' have symptoms of allergic rhinitis may develop asthmatic symptoms if exposure continues.[165,168,178,201,206] In the most unfavourable situation, allergic symptoms do not disappear after exposure has entirely ceased.[5,19,47,49,97,108,146,168,186,198,201,202,202,214,215,265]

9.3.7 *The cost of the programme must be proportionate to the overall health care costs and benefits*

Before a decision can be made regarding the introduction of periodic screening, clarity is required concerning the relationship between the net costs and the attainable health benefit. Hence, a cost-effectiveness analysis is required: the health benefit attainable through periodic screening needs to be weighed up against the financial impact of introducing such a programme.[87] The health benefit obtainable through screening may be expressed in various ways, *e.g.* the decrease of the number of cases of occupational asthma, the number of problem free days, QALYs or DALYs. The financial impact is the product of the extra costs involved in setting up and operating a screening programme, and the anticipated increase or decrease in other costs incurred within and outside the health service. Screening can affect direct health care costs by influencing the need for hospitalisation, other medical treatments and medication use. It can also impact on indirect costs outside the health care system, such as the economic consequences of sickness absenteeism, work disability and productivity.

If cost-effectiveness analysis indicates that the cost of a programme exceeds the potential economic savings, it is necessary to consider whether the additional cost is justified. Any judgement on this score depends largely on one's viewpoint. Various viewpoints may be taken, such as those of the individual worker, the employer, the government, and the health insurer. Introducing a screening programme may, for example, benefit the health insurer by reducing medical

consumption; yet it may have undesirable economic implications for the company that pays for the programme, but does not profit from the reduced medical consumption. For this reason, it is best to use a societal viewpoint for the economic evaluation of health interventions, *i.e.* to take account of all significant costs and benefits, regardless of who incurs the costs or reaps the benefits.[232]

A cost-effectiveness analysis necessitates a large body of data, preferably from long-term randomised clinical trials (RCTs). However, in the occupational health service, which is characterised by a decentralised structure and control mechanisms, such trials are time-consuming, costly and difficult to perform. To the best of the committee's knowledge, no such long-term studies involving thorough cost-benefit evaluation have been undertaken in respect of screening for work-related inhalant allergies.

In view of the lack of good RCT data, simulation models could be used to obtain information on potential health benefits in relation to certain costs. Such models combine data from various studies and take account of effects occurring well outside the original study periods. The Markov model is particularly useful as a means of calculating the ongoing risk of a disease – especially an episodic disease – developing and worsening over a long period.[232]

An interesting example is given in an American model study.[148,275] The study focused particularly on occupational asthma in a group of people working with isocyanates. The researchers compared two health prevention methods: the established prevention method (waiting until a worker sought medical advice as he or she felt appropriate, also known as opportunistic screening) and an alternative method (actively making annual screening available in order to identify workers sensitised by occupational exposed to isocyanates). Both scenarios were evaluated using the Markov model for a period of ten years, in relation to a hypothetical cohort of 100,000 exposed workers. Using data from various cross-sectional and cohort studies, estimates were made of the likelihood of sensitisation, progression from sensitisation to the development of asthma and other symptoms, health improvement following removal from the workplace, and the various consequences in terms of absenteeism and disability. These data formed the basis of the mathematical simulation model, with which the anticipated cost-effectiveness of each intervention method was calculated. Over a period of ten years, annual screening (by questionnaires and spirometric examination) yielded a reduction of 683 cases of asthma, 3.3 million symptom-free days and thirty-one cases of disability. The health benefits were associated with financial savings of 44 million dollars, at a cost of more than 80 million dollars. Thus, the researchers put the cost of a healthy life-year gained at 24,000 dollars.

The US data are not directly applicable in the Netherlands. An important consideration when performing a cost-effectiveness analysis is how to quantify the costs and benefits. In the American study, the impact of asthma-related disability on workers' income was assumed to be constant throughout the study period, whereas worker mobility makes it plausible that the impact would in fact be felt for a much shorter period. In addition, the cost of absenteeism was quantified by the researchers in a way that reflected the US social security system, and would be inappropriate in the Netherlands. The cost-effectiveness is also strongly influenced by the assumptions made regarding the natural course of occupational asthma and the health impact of the modelled forms of intervention. The American study referred to shows that the incidence of specific sensitisation to isocyanates may vary between 1.9 and 5.3% a year. Where the actual incidence lies within this range has major implications for the cost-benefit ratio.

The American study nevertheless illustrates that introducing periodic screening for occupational asthma might be beneficial. However, no good cost-effectiveness studies have been performed in the Netherlands in connection with the introduction of periodic screening for allergic sensitisation and respiratory disorders. Furthermore, there are no validated simulation models. Consequently, although the committee believes that periodic screening may be cost-effective, it cannot be certain that this is actually the case.

9.3.8 *Case finding should be a continuing process and not a once and for all project*

In those cases where periodic screening is desirable, consideration should be given to the time interval to which screening tests should be repeated. If the frequency of screening is too low, the programme will in practice tend to detect mainly people who have already developed the very problems that it is designed to prevent. The appropriate screening frequency depends on various factors, including the interval between initial exposure and sensitisation, and the interval between sensitisation and the manifestation of respiratory allergies.

With regard to the time span between first exposure and development of allergic sensitisation, this can be very short: sensitisation can occur on the first day of exposure. In practice, however, this will not necessarily be the case. A number of prospective studies have been published, in the context of which new cases of specific sensitisation – and even respiratory allergy – were observed in people who had been working in the relevant industry for only six months (bakers, laboratory animal carers, people working with acid anhydrides).[52,54,61,76,189,273] Recent data from a prospective study, in which workers were followed up for

more than ten years, appear to indicate that – certainly among laboratory animal carers – the risk of being sensitised remains equally high for several years following initial exposure. Whether a person is sensitised very quickly or only after the passage of considerable time, or even will never become sensitised, depends of person-related factors and the individual exposure circumstances.

The committee accordingly concludes that the timing of screening and the optimal time interval should be considered on a case-by-case basis. However, it is assumed that the periodicity appropriate for the detection of specific sensitisation will generally be higher than normal in the context of, for example, periodic occupational health checking; thus a screening interval of six months to a year is more likely to be suitable than an interval of two to three years.

9.3.9 Conclusions

In practice it should be taken into account that cases of allergic sensitisation does occur, and that if exposure is continued, allergic airway disorders can develop. In view of the prognosis if exposure is continued, and the fact that in some occupational groups the prevalence of allergic airway disorders is high, the committee considers periodic screening on allergic sensitisation a meaningful point of departure. Yet, under the condition that workers are properly informed about the potential consequences of a positive outcome.

The committee, however, makes some comments on the feasibility. An important condition is, namely, that allergic sensitisation can be assessed by accurate and reliable tests. For certain well-known allergens, such as those found in flour dust, the urine of laboratory animals and in latex, such tests are available. However, there are other allergens for which tests still need to be developed. These include allergens that cause sensitisation by triggering a non-IgE-mediated immune response. As long as these tests are not available, periodic screening may focus on the detection of early symptoms and signs caused by allergy (see section 9.5).

Another criterion is that it is ascertained whether the investment of the introduction of periodic screening is acceptable. In view of the number of cases of allergic respiratory symptoms in certain occupational groups, the committee assumes that screening is likely to be cost-effective. However, there is insufficient evidence to confirm this statement, because up to now no thorough studies were performed in the Netherlands on the cost-effectiveness.

Given these remarks, the committee judges that it is worth to consider the introduction of periodic screening in addition to other tools available in managing exposure. Basically, periodic screening could be fairly and straightforwardly

incorporated into the already existing, and statutory regulated periodic occupational health examination. The feasibility of periodic screening on allergic sensitisation, and what else is needed to comply with the most important criteria, should however be judged case by case.

9.3.10 *Screening for personal risk factors*

In principle, everyone who comes into contact with inhalant allergens should be offered periodic screening. However, logistic difficulties or other problems may make universal screening very expensive in certain circumstances. This might be the case, for example, with people working in small traditional bakeries scattered around the country. Under such circumstances, the committee believes that prognostic modelling would facilitate the control of both cost and effectiveness. Using a prognostic model in conjunction with a questionnaire would enable distinction between high-risk and low-risk workers within a company or industry. This in turn would mean that screening could be targeted on those individuals who were at most risk. Prognostic models for laboratory animal carers and bakers are currently being developed and their predictive value and effectiveness tested.[169-171]

In the context of discussions surrounding the risk of illness associated with occupational exposure, it has sometimes been suggested that efforts should be made to identify people who are particularly susceptible to allergic disorders before they begin work in a setting where they will be exposed to allergens. Such screening might be incorporated into pre-employment medical checks, so that highly susceptible people can be informed about the risks or are not appointed at all. According to the Dutch statutory regulations, pre-employment medical checks can only be performed if these meet certain conditions. One is that the risks on health and safety cannot be reduced with current measures. This means that first of all, the risks which are associated with certain jobs, as much as possible need to be prevented by taking preventive measures.

Setting aside any other possible reservations about such an approach, it is scientifically doubtful how effective it could be as a means of identifying those at most risk of developing inhalant allergies, since the predictive value of the immunological tests for personal risk factors, such as atopy and such like, is very small.[59,246,255] For instance, a considerable number of non-atopic subjects are being sensitised, and a considerable number of atopic subjects will never be sensitised for the allergen in question. Therefore, identification of such risk factors, with the purpose of not appointing, should be considered cautiously.

9.4 Other preventive tools available to the occupational healthcare sector

The committee emphasises that in those cases that secondary prevention is not feasible, for instance because no suitable immunological screening tests are available, as a point of departure tertiary prevention could be considered. Also identifying subjects with (non)specific symptoms which point to allergic airway disorders, and who are working in industries where exposure to allergens is likely, will improve the prognosis of those subjects, assuming that clear diagnostic courses are available. What the best tactic is, active detection or offering easily accessible consultations (opportunistic screening), is unclear, because no comparative research have been performed yet. In any case, physicians should be aware of the existence of occupational airway allergies in certain industries.

Furthermore, the committee would highlight the fact that various other tools are available to the occupational healthcare sector, whether used on their own or in conjunction with periodic screening. These tools and the order of implementation are established in the occupational hygienistic strategy. The highest priority in this strategy is removal or reduction of sources that causes the problem. In the second and third step, technical measures, such as separation between source and humans or installation of exhaust hoods, and collective organizational and/or procedural measures are implemented. Finally, personal protective equipments could be introduced, such as wearing masks.

9.5 Conclusions

The committee considers periodic screening on allergic sensitisation a meaningful point of departure. Yet, under the condition that workers are properly informed about the potential consequences of a positive outcome.

The committee, however, makes some comments on the feasibility, because for a good introduction certain criteria apply, which are not always met. One concerns the lack of availability of reliable immunological tests. As long as these tests are not available, periodic screening may focus on the detection of early symptoms and signs caused by allergy. The other that no data are available on cost-effectiveness in the Dutch situation.

Given these remarks, the committee judges that it is worth to consider the introduction of periodic screening in addition to other tools available in managing exposure. At the moment the best would be to judge the feasibility of periodic screening on allergic sensitisation case-by-case. Basically, periodic

screening could be fairly and straightforwardly incorporated into the already existing, and statutory regulated periodic occupational health check. Furthermore, in controlling risks on health damage in the workplace, it is of importance to bear in mind other preventive measures, which are available to the government and business community.

Chapter **10**

Answers to the Minister's questions

The most important conclusions are summarised in this chapter, and the ministers' questions are answered individually. The chapter ends with a summary of recommendations regarding further research.

10.1 What is the best way of calculating exposure limits for inhaled allergens and thus of managing the risk of allergic disorders in workers who experience occupational exposure?

Sensitisation is the best basis for the calculation of recommended OELs

Where allergic respiratory disorders are concerned, the committee is of the opinion that data on allergic sensitisation provide a better starting point for the calculation of OELs than data on the manifestation of symptoms, since allergic sensitisation plays a crucial biological role and is a prerequisite for the development of allergy. Allergic respiratory symptoms cannot develop if a person is not sensitised. The committee's recommendation is based primarily on the latter consideration, and the precautionary assumption that, in the event of continued exposure, almost all sensitised workers will ultimately develop allergic respiratory disorders.

A health-based recommended occupational exposure limit

A health-based recommended occupational exposure limit is a specification of the level of exposure to an airborne substance, which may be regarded as a threshold level, at or below which it may reasonably be expected that there is no risk of adverse health effects. Current scientific knowledge regarding the immunological mechanisms involved in allergy suggests that a threshold level does exist for allergens. This implies that health-based occupational exposure limits can be calculated for allergens using the same procedures and methods as those used for other non-carcinogenic substances. Hence, the first step towards calculating such a limit is to determine whether, in the given instance, it is possible to use a method such as the common no-observed-adverse-effect-level method, the benchmark dose method, or another similar statistical model for human data.

However, the committee believes that, where most allergens are concerned, it will not be possible to calculate a reliable health-based occupational exposure limit by any such method. The reason being that, in most cases, the threshold level will be too low to discern using the techniques presently available. To get an idea of where a threshold level for allergens might lie, the committee evaluated some exposure and response data from observational and animal studies. Considering the great variety of allergens that can be present in the workplace, surprisingly few data are available. These data reveal a varied picture. For instance, the large body of data available on (wheat) flour dust allergens did not show a threshold level for such allergens, but there does appear to be a threshold for soluble platinum salts.

The non-use of valuable data regarding higher levels of exposure to certain allergens, for which reliable health-based recommended OELs cannot be calculated, strikes the committee as regrettable in view of the health problems experienced by workers as a result of exposure to such allergens.

Reference values as an alternative approach

The committee has therefore explored the possibility of using an alternative approach for this group of allergens. This approach involves assuming that no threshold exists and adopting the methodology used for certain carcinogens (linear extrapolation or a benchmark dose method). The products of this approach are reference values, which correspond to predefined accepted levels of risk of allergic sensitisation. These reference values can then be used as a basis for the definition of occupational exposure limits. The committee recommends that the predefined accepted level of risk should take account of the background preva-

lence of the allergen in question. However, the final decision on the predefined accepted level of risk will also depend on policy and social considerations.

The committee would emphasise that, if one applies a standard based on a reference value, it is inevitable that some workers will still develop allergic respiratory disorders. The reason being that a standard set in the manner described will define a level of exposure, which carries an acceptable risk; hence, the development of new allergy cases will be tightly controlled but not entirely prevented. If someone is unlucky – perhaps insofar as he or she is hypersensitive or insofar as other unfavourable factors are at work – he or she may still become sensitised and go on to develop an allergic respiratory condition.

The contribution of personal and other environmental factors on the development of allergy

Exposure to an inhalant allergen is the basic prerequisite for allergic sensitisation and the development of associated respiratory conditions. However, various other factors may influence the occurrence of such phenomena. These include personal factors, such as genetic predisposition, and other environmental factors, such as the circumstances of exposure and combined exposure. Some of these factors have been fairly well described, but the extent of their influence on the development of allergy (caused by occupational exposure) remains unclear, simply because not enough is yet known. Nevertheless, the identification of risk factors is important not only for the proper assessment of proposed occupational exposure limits, but also for the acquisition of a good overview of the risk factors that exist. Such factors can then be taken into account when seeking to improve working conditions.

Selection of the critical adverse health effect

This report is concerned exclusively with respiratory allergies. However, in addition to their sensitising effects, allergens can have irritant, carcinogenic, neurotoxic or other effects on the respiratory system or other systems in the body. The existence of such additional toxic effects needs to be considered on a case-by-case basis and an occupational exposure limit defined accordingly. Setting an occupational exposure limit at a level suitable for the prevention of sensitisation is appropriate only if by doing so it is clear that other serious adverse health effects will also be prevented. If that is not the case, the limit should be based on another, more sensitive or relevant effect.

10.2 If the occupational inhalation of allergens, regardless of the level of exposure, entails a risk of sensitisation or allergy development, would periodic screening for the illness or its precursors be a desirable and effective means of preventing aggravation?

Although occupational exposure limits are useful as a means of protecting workers' health, it should be recognised that their application will not prevent all cases of allergic sensitisation and respiratory disorder. One additional option available to the government and the business community is the early detection of sensitised workers, by means of periodic screening, for example.

In view of the prognosis associated with continued exposure and the high prevalence of allergic respiratory disorders in some occupational groups, the committee considers periodic screening for allergic sensitisation to be a potentially valuable tool – provided that workers are properly informed about the potential consequences of a positive test result.

The committee makes some comments on the feasibility, however. For instance, periodic screening is of value only where accurate and reliable tests are available for the detection of allergic sensitisation to the relevant allergen. Such tests *are* available for certain well-known allergens, such as those found in flour dust, the urine of laboratory animals and in latex. Where other allergens are concerned, however, such tests still need to be developed. The allergens in question include those that can cause sensitisation by triggering a non-IgE-mediated immune response. As long as these tests are not available, periodic screening may focus on the detection of early symptoms and signs caused by allergy.

Furthermore, periodic screening is appropriate only if the cost is reasonable in relation to the benefit. In view of the number of cases of allergic respiratory symptoms in certain occupational groups, the committee assumes that screening is likely to be cost-effective for such groups. However, there is insufficient evidence to confirm that this is indeed the case, because no thorough cost-effectiveness studies have yet been performed in the Netherlands.

In conclusion, the committee judges that it is worth to consider the introduction of periodic screening in addition to other tools available in managing exposure. Basically, periodic screening could be fairly and straightforwardly incorporated into the already existing, and statutory regulated periodic occupational health examination. The feasibility of periodic screening on allergic sensitisation, and what else is needed to comply with the most important criteria, should however be judged case-by-case.

10.3 Answers to the minister's specific questions

The minister's questions are answered by the committee in the body of this advisory report. However, for the sake of convenience, direct answers to the individual questions are also presented below.

On average, how serious are and what is the prognosis associated with: a) sensitisation and b) the disorders (in particular occupational asthma) caused by allergens?

Allergic sensitisation is not in itself a health complaint. However, sensitisation is a condition, which can lead to serious and irreversible health problems, such as allergic asthma and allergic rhinitis. These can lead to permanent changes to the respiratory tract and to associated complaints, which in some cases persist even when exposure has completely ceased.

Is there a critical effect upon which a control system should be based, and what are the arguments in favour of such an approach?

From a health-protection viewpoint, a control system should be based on the prevention of allergic sensitisation. The reason being that sensitisation plays a crucial biological role and is a prerequisite for the development of allergy. Furthermore, the committee assumes that, in the event of continued exposure, almost all sensitised workers will ultimately develop allergic respiratory disorders.

What standardisation systems may be used in order to prevent or control the occurrence of sensitisation and the development of allergic disorders due to occupational exposure to allergens? What are the advantages and disadvantages of the various systems and how do they compare to one another? What relevant international experience, developments and guidance can be identified?

Regarding the occupational situation, standardisation systems for allergens can be based on health-based recommended occupational exposure levels or reference values for allergic sensitisation. Such levels and values can be calculated in accordance with a procedure and using methods, which are widely used in the regulation of work-related exposure to substances.

The main difference between a health-based recommended OEL and a reference value is that the former corresponds to an exposure level, at or below which it may reasonably be expected that there is no risk of adverse health effects. By contrast, a reference value corresponds to a predefined accepted extra risk of allergic sensitisation.

So far known, no thorough evaluations have been performed in other countries with a view to identifying the best standardisation system for allergens. Generally, exposure limits are calculated using a methodology similar to that used for health-based recommended OELs. However, the point should be made that an exposure limit does not afford complete protection. The European Union's SCOEL allows for exposure limits for sensitising substances to be set on the basis of reference values. In the United Kingdom, the prevention or control of allergic sensitisation and respiratory disorders is based on what is technically practicable (comparable with the ALARA principle; as low as reasonably achievable), rather than on health-based considerations.

In addition to standardisation, some European countries use systems of sensitisation notation, which involve the provision of warnings regarding sensitising substances, associated with advice to the effect that employers and employees should take measures to prevent allergic sensitisation.

What system would you recommend using, in view of the policy principles that apply in the Netherlands and internationally?

The first step should be to establish whether an occupational exposure limit can be assessed on the basis of a health-based recommended occupational exposure limit. A limit of the latter kind is calculated in accordance with a procedure and using methods, which have been described and discussed in detail in the scientific literature.

However, in the case of an allergen, for which no health-based recommended OEL can be specified using the techniques presently available, the committee recommends setting a limit on the basis of reference values.

Where insufficient data are available to determine reference values either, the first step should be to undertake additional research in order to acquire response data for the lowest exposure levels. In the interim, an exposure limit could be based on data concerning the development of allergic respiratory symptoms. The committee emphasises, however, that from a health perspective this is not ideal.

Assuming that, at least where some allergens (such as flour dust) are concerned, no health-based safe exposure level can be determined, is it possible or desirable

to draw up additional guidance regarding periodic screening of the risk groups for relevant health indicators? If so, under what circumstances is such screening advisable? What form should any such periodic screening take, and how (cost-) effective is it likely to be?

The committee considers periodic screening for allergic sensitisation to be a potentially valuable tool – provided that workers are properly informed about the potential consequences of a positive test result.

The committee makes some comments on the feasibility, however. To guarantee a successful introduction of periodic screening a number of criteria are set up. One of these is the availability of reliable immunological tests. For certain allergens, such as those found in flour dust, latex and in the urine of experimental animals such test exist already, but for other allergens they still need to be developed. As long as these tests are not available, screening could be based on early diagnosis of allergen-induced respiratory allergy symptoms. However, from the health-based view this is not ideal. Another criterion is that clarity is required concerning the relationship between the net costs and the attainable health benefit. Regarding occupational exposure to allergens in the Netherlands, this has not yet been investigated. Therefore, it is unclear to what level periodic screening in the workplace will be cost-effective.

In conclusion, the committee judges that it is worth to consider the introduction of periodic screening in addition to other tools available in managing exposure. Basically, periodic screening could be fairly and straightforwardly incorporated into the already existing, and statutory regulated periodic occupational health examination. The feasibility of periodic screening on allergic sensitisation, and what else is needed to comply with the most important criteria, should however be judged case-by-case.

10.4 Research requirements

The committee notes that there is a relatively paucity of data regarding occupational exposure, allergic sensitisation and the development of respiratory disorders. At the moment, reliable health-based recommended occupational exposure limits or reference values can be calculated only for a small number of allergens. It is a source of concern to the committee that the risks associated with exposure to many allergens cannot easily be controlled by the application of exposure limits, because allergy is a serious problem in some occupations.

There is consequently a need for research of various kinds. High priority should be given to collecting exposure and response data, particularly regarding

relatively low levels of exposure. Such data collection must be accompanied by the development of standardised and validated exposure methodologies and immunological tests, whose use in the occupational health care sector is practicable. The development of immunological tests depends upon clarification of the relevant immunological effect mechanisms, particularly as associated with low molecular weight allergens.

Finally, there is a need for information regarding effects and suitability in terms of health benefits associated with the introduction of periodic screening.

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Annexes

Annex **A**

Request for advice

Date of request: 12 April 2005
Reference: ARBO/P&G/2005/24294

Dear Mr Knottnerus,

I am writing to ask the Health Council to advise me regarding the most appropriate standardisation method to use in relation to occupational exposure to allergens. This request is made in the context of the "Health and Environment: Working Conditions" element of your work programme.

Background

The immediate trigger for this request is the recent publication of your advisory report on the determination of the health effects of occupational exposure to wheat and related cereal flour dusts (for brevity, referred to simply as "flour dust")*. The critical effect used for risk estimation in the context of the latter report is hypersensitivity (sensitisation). The Council opted to use this special approach to risk estimation because it was not possible to determine a level of exposure below which sensitisation to this allergen did not occur. It is, however, possible to make a quantitative estimate of the risk of sensitisation at a given level of exposure. Most people who become sensitised will develop an allergic condition if exposure continues. I am grateful for the thoroughness and critical approach displayed by the Council in the preparation of the advisory report in question.

* Wheat and other cereal flour dusts. An approach for evaluating health effects from occupational exposure, Health Council DECOS, 2004; publication no. 2004/02OSH.

There is good reason to believe that flour dust is not the only allergen for which the determination of a threshold level poses considerable difficulties. A report on allergies and asthma associated with working with enzymes published by IRAS and TNO concluded, for example, that no threshold level could be determined for the enzyme alpha-amylase*.

According to the Alert Report on Occupational Diseases 2003, published by the Netherlands Centre for Occupational Diseases (NCvB), contact eczema and occupational asthma are the most frequently reported illnesses attributable to occupational exposure**. Allergens play a major role in the causation of these disorders. The report states that while skin contact with allergens can be prevented to a significant extent, if not entirely, by information provision and skin protection, the prevention of exposure to various inhalant allergens is more difficult. This is all the more problematic in view of the fact that it now seems increasingly likely that it is not possible to define no-effect levels for allergens. This poses particular challenges for the determination of occupational exposure limits. The NCvB concludes that there is a need for clarity concerning the basis on which acceptable exposure levels and guidance on working with allergens should be formulated. Clarity concerning these matters is particularly important for occupational health professionals who support employers in the protection of their workers' health.

I should therefore be grateful if you would inform and advise me regarding this issue.

Questions

In your report, please address the following questions:

1 On average, how serious are and what is the prognosis associated with: a) sensitisation and b) the disorders (in particular occupational asthma) caused by allergens?
2 Is there a critical effect upon which a control system should be based, and what are the arguments in favour of such an approach?
3 What standardisation systems may be used in order to prevent or control the occurrence of sensitisation and the development of allergic disorders due to occupational exposure to allergens? What are the advantages and disadvantages of the various systems and how do they compare to one another? What relevant international experience, developments and guidance can be identified?
4 What system would you recommend using, in view of the policy principles that apply in the Netherlands and internationally?
5 Assuming that, at least where some allergens (such as flour dust) are concerned, no health-based safe exposure level can be determined, is it possible or desirable to draw up additional guidance

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* *Allergie en astma als gevolg van het werken met enzymen* [Allergy and asthma attributable to working with enzymes], 2004, Heederik *et al.* IRAS University of Utrecht and TNO Nutrition, Zeist.

** Alert Report on Occupational Diseases, 2003, Netherlands Centre for Occupational Diseases.

regarding periodic screening of the risk group for relevant health indicators? If so, under what circumstances is such screening advisable? What form should any such periodic screening take, and how (cost-)effective is it likely to be?

In your report, please address at least the following:

- The latest scientific thinking and knowledge regarding the occurrence of sensitisation and allergic disorders attributable to occupational exposure to substances in the air or by skin contact, including:
- The relationship between sensitisation and allergic disorders
- The influence of atopy on this relationship
- The presence or absence of a quantitative relationship between the level of exposure and the occurrence of sensitisation and allergic disorders
- The differences between high-molecular-weight and low-molecular-weight allergens
- If relevant, the influence of compound exposure involving several allergens or allergens and enhancers and inhibitors
- The prevalence of sensitisation and allergy in the population

In your report, you may wish to take account of scientific thinking elsewhere in the EU, by for example consulting with colleagues in other countries.

Finally, in view of the anticipated revision of the system of occupational exposure limits, I should be grateful if you would address this request for advice as a matter of priority. Please submit your report no later than April 2007.

Yours faithfully,
State Secretary for Social Affairs and Employment,
(signed)
(H.A.L. van Hoof)

Annex **B**

The committee

- T. Smid, *chairman*
  professor of working conditions, Free university, Amsterdam; and,
  occupational hygienist/epidemiologist, KLM Health Services, Schiphol-Oost
- E.C. van den Aker, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- A. Burdorf
  epidemiologist, Department of Public Health, Erasmus MC, University Medical , Center Rotterdam, Rotterdam
- R. Gerth van Wink
  professor of allergology, Erasmus MC, University Medical Center Rotterdam, Rotterdam
- D.J.J. Heederik
  professor of risk assessment in occupational epidemiology, Institute for Risk Assessment Sciences, Utrecht
- G.F. Houben
  Toxicologist, TNO Quality of Life, Zeist
- H. Van Loveren
  professor of immunotoxicology, University of Maastricht; Laboratory for Toxicology Pathology and Genetics, National Institute of Public Health and the Environment, Bitlhoven

- T.M. Pal
  occupational physician, Netherlands Center for Occupational Diseases, Amsterdam
- G.B.G.J. van Rooy
  occupational physician, Netherlands Expertise Centre for Occupational Respiratory Disorders; Institute for Risk Assessment Sciences, Utrecht; and, Arbo Unie, Utrecht
- J.S. van der Zee
  lung specialist, Academic Medical Center, Amsterdam
- dr. J.M. Rijnkels, *scientific secretary*
  Health Council, The Hague

The committee has consulted R Pieters, immunotoxicologist at the Institute for Risk Assessment Sciences in Utrecht, as external expert.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Comments on the public review draft

A draft of the present advisory report was released in 2007 for public review. The following organisations and persons have commented on the draft document:

- D. Zumwalde, National Institute for Occupational Safety and Health, USA
- H. Greim, German MAK-committee, DFG, Germany
- E. González-Fernández, Spanish Ministry of Social Affairs and Employment, Spain
- M. Elema, Productschap Granen, Zaden en Peulvruchten, the Netherlands
- S. Cochrane, Unilever, the United Kingdom
- C. Rodriguez, Procter & Gamble, Belgium
- M. Jeffs, ALIPA and ISOPA, Belgium
- J. Arts and F. Kuper, TNO Quality of Life, the Netherlands
- P. Leijh, Nederlandse Federatie van Universitaire Centra, the Netherlands
- H. Levie, VSNU, association of universities, the Netherlands

Annex **D**

Prevalences of work-related allergic respiratory disorders

Table D.1 List of sensitising substances, estimated prevalence of asthma, rhinitis or specific sensitisation and assessment of the quality of published research material, estimated size of the Dutch population and estimation of the extent of the risk problem (after Heederik *et al*., 1999).[108]

High molecular weight allergens						
Category	Allergen	Prevalence	Quality of studies (1)	Population at risk (2)	Risk (3)	Occupational group(s)
Allergens of animal origin	Laboratory animals	3-12%	A	B	A*	Laboratory animal workers, zoo workers, animal sanctuary workers
	Cows, pigs	?	C	A	B/C	Farm workers, meat processors
	Poultry	?	C	A	B/C	Farm workers, meat processors
	Fish	8%	A/B	C	C	Fish processors
	Prawns, crabs	2-36%	A/B	B	B	Fish processors, fish breeders
	Wool	?	?	C	C	Textile workers
	Silk	0.2-34%	A/B	C	C	Textile workers
Allergens of insect origin	Mites	12-33%	B	A	B	Farm workers, bakers, storage and transfer workers
	Mealworms	?	C	C	C	Fish breeders
	Locusts	26-60%	B	C	C	Laboratory animal workers
	Fruit flies	32%	B	B	B	Laboratory animal workers
Allergens of plant origin	Grain (dust)	?	B	A	B	Bakers, millers, storage and transfer workers
	Wheat, rye, soya flour	2-7%	A	A	A	Bakers, millers
	Tobacco	69%	B	B	B	Tobacco processing workers
	Tea	?	B/C	C	C	Food processing workers
	Seaweed (alginate binder)	4%	?	C	C	Food processing workers, pharma-ceutical and textile workers

	Herbs (*e.g.* coriander, garlic, cinnamon, saffron)	?	C	B/C	C	Food processing workers
	Flowers and plants (*e.g.* gypsophila, freesia, amaryllis, club moss, briar rose, fig, capsicum)	7-9%	A/B	B/C	B	Plant growers, plant care workers, pharmaceutical workers
	Green coffee beans	9-34%	A/B	C	C	Food processing workers
	Castor beans (and oil)	14%	A/B	C	C	People working in production of cosmetics, nylon, explosives, paint, ink
	Cocoa, chocolate	5%	A/B	A/B	B	Bakers, food processing workers
	Hazelnuts	6% SPT+	B	A/B	B	Bakers, food processing workers
	Almonds	6% SPT+	B	A/B	B	Bakers, food processing workers
	Latex (*Hevea brasiliensis*)	2-13%	A/B	A	A	Health care practitioners
Allergens of Fungi	Aspergillus niger	2-5%	A/B	C	C	Biotechnological industry
	Mushrooms (soup powder)	?	C	C	C	Food processing workers
Proteins and Enzymes	α-amylase (from fungi)	2-15% SPT+/IgE+	A/B	A	A	Bakers
	Amyloglucosidase and hemicellulase	?	C	A	B/C	Bakers
	Milk protein	2% IgE+	B	A/B	B	Bakers
	Lactase	3%	B	C	C	Pharmaceutical workers
	Trypsin	21%	B	C	C	Dairy, pharmaceutical, plastics industry workers
	Pancreatine	?	C	C	C	Pharmaceutical workers
	Papain	29%	B	B	B	Pharmaceutical workers, food processing workers, bakers, laboratory technicians
	Bromelain ("meat tenderiser")	11%	B	B/C	B/C	Pharmaceutical workers and food processing workers
	Bacillus subtilis enzymes (alcalase, savinase)	3%	A	B	B	Soap production workers
	Esperase	5% IgE+	?	?	?	Soap production workers
	Phytase	?	?	?	?	Livestock workers
	Egg protein	7%	A/B	A/B	B	Food processing workers
Polysaccharides	Acacia (Arabian gum)	9-19%	B	C	C	Pharmaceutical and food processing workers, hairdressers, print workers
	Guar gum (*Cypamopsis tetragonolobus*)	2%	A/B	C	C	Pharmaceutical and food processing workers, carpet makers
	Karaya	4%	?	C	C	Hairdressers, print workers

Low molecular weight allergens

Category	Allergen	Prevalence	Quality of studies (1)	Population at risk (2)	Risk (3)	Occupational group(s)
Metals (salts)	Platinum salts (mainly halides)	9-29%	A/B	B/C	B	Metal workers, welders, catalyst production workers
	Cobalt	1-5%	A	C?	B/C	Metal workers, welders, diamond cutters
	Nickel salts (mainly sulphates)	?	C	A?	B/C	Metal workers, welders
	Chromium salts	?	C	B?	B/C	Metal workers
Anhydrides	Phthalic acid anhydride (PA)	8-18%	A/B	A?	A	Plastics, synthetics and pharmaceutical workers
	Methyl tetrahydrophthalic acid anhydride (MTHPA)	11%	A/B	A?	A	Synthetics workers (epoxy resin producers)
	Trimellitic acid anhydride (TMA)	2-10%	A/B	A?	A	Plastics, synthetics, paint, paper and textiles workers (epoxy resins, PVC, fillers)
	Tetrachlorophthalic acid anhydride (TCPA)	2%	A	A?	A	Synthetics workers (alkyd, epoxy resin production)
	Hexahydrophthalic acid (HHPA)	15-28%	A/B	A?	A	
	Himic anhydride (HA)	15%	B	?	B	Flame retardant workers
	Pyromellitic acid dianhydride	?	C	?	C	Synthetics workers (epoxy resin production)
Isocyanates	2.4- and 2.6-toluene diisocyanate (TDI)	1-10%	A	A	A	Electronics, rubber, synthetics, metal and foam production workers, spray paint shop workers
	Methylene diphenyl diisocyanate (MDI)	13-27%	A/B	A	B	Electronics, rubber, synthetics, metal and PUR foam production workers, spray paint shop workers
	Hexamethylene diisocyanate (HDI)	?	C	?	C	Spray paint shop workers
	Naphthalene diisocyanate (NDI)	?	C	?	C	Spray paint shop workers
	Isophorone diisocyanate (IPDI)	?	C	?	C	Spray paint shop workers
Amines	Ethylene diamine (EDA)	?	C	?	C	Photographic materials, plastics, rubber, and cosmetics production workers
	Hexamethylene tetramine	?	C	?	C	Varnish and cosmetics production workers
	Mono-ethanol amine	?	C	?	C	Cosmetics production workers
	3-dimethyl amino-propylamine	12%	B	?	B	Ski and other production workers
	Piperazine dihydrochloride	11%	A/B	?	B	Pharmaceuticals and chemicals workers
	N-methyl morpholine	17%BHR+	B	?	B	
	p-Phenylene diamine	37%	A/B	?	B	Fur industry workers, hairdressers

Acrylates	Alkyl cyanoacrylates	?	C	B	B/C	Glue production workers
	Methyl methacrylate	?	C	B	B/C	Health care practitioners (e.g. dental technicians), cosmetics production workers
Allergens of tree (wood) origin	Western Red Cedar (plicatic acid)	3-4%	A	B/C	B	Sawmill workers, wood processors, furniture makers
	Eastern White Cedar	4-7%	A	C	B/C	Sawmill workers, wood processors, furniture makers
	Colophonium	4-21%	A/B	A/B	B	Welders, electronics workers
	Other tree species (*e.g.* fernambouc, cedar, spruce?)	?	B/C	A	B	Sawmill workers, wood processors, furniture makers
Pharmaceu-tical products	Antibiotics (*e.g.* penicillins, cephalosporins, phenyl glycinic acid chloride, spiramycin)	7-29%	A/B	A/B	B	Pharmaceutical workers, health care practitioners, intensive livestock farm workers?
	Other pharmaceu-ticals (*e.g.* psyllium, ipecacuanha, cimetidine, opiates)	4-48%	A/B	A/B	B	Pharmaceutical workers, health care practitioners
Other	Disinfectants (*e.g.* glutaraldehyde, chloramine T)	89%?	B	A	B	Cleaners, health care practitioners, pig farm workers
	Azodicarbonamide	19%	B	?	B	Plastics and rubber workers
	Diazonium salt	4-56%	B	?	B	Photocopier paper (and polymer?) production workers
	Reactive dyes (azaquinone, anthraquinone, methyl blue, black GR)	4-8%	A	?	B	Textile workers
	Persulphate	2-17%	A/B	A/B	B	Chemicals workers, hairdressers

(1) The studies referred to have been quality-assessed and categorised as follows:
A: epidemiological study, diagnosis of occupational asthma by bronchial provocation test
B: epidemiological study, diagnosis of occupational asthma by questionnaire/other
C: only clinical and/or multiple case studies

(2) The size of the population at risk has been estimated and categorised as follows:
A: > 10,000 people
B: 1,000 - 10,000 people
C: 1 - 1,000 people

(3) The letter in the final column is a compound index covering the extent of the risk (prevalence or incidence), the quality of the information and the estimated size of the population at risk. This index is used to assess the priority of the allergen, in view of the risk and the size of the exposed population.

* Laboratory animal allergens are placed in category A, even though the population at risk is relatively small, because the high potency of the allergens means that they can cause sensitisation of the respiratory tract even at very low concentrations. Furthermore, insight into the problem in the Netherlands is relatively good and the quality of the studies is high.

Table D.2 Incidences and prevalences per allergen (after Heederik *et al*., 1999).[108]

Laboratory animal allergens	
Number of workers in the Netherlands	4,600
Incidence of occupational asthma (based on SWORD; cases/yr)	1
Prevalence of sensitisation (SPT+, IgE; cases)	300 - 1,900
Prevalence of allergic disorders (number)	500 - 1,500
Prevalence of asthmatic disorders (number)	150 - 550
Incidence of sensitisation (cases/yr)	100 - 200
Incidence of allergic respiratory disorders (cases/yr)	100 - 150
Latex	
Number of workers in the Netherlands	200,000
Incidence of occupational asthma (based on SWORD; cases/yr)	3
Prevalence of sensitisation (cases)	6,000 - 34,000
Prevalence of allergic respiratory disorders (cases)	5,000 - 26,000
Incidence of sensitisation (cases/yr)	1,800
Flour	
Number of workers in the Netherlands	32,000
Incidence (based on SWORD)	9 - 13
Prevalence of sensitisation (cases)	1,600 - 8,000
Prevalence of allergic disorders (cases)	1,600 - 8,000
Incidence of sensitisation (cases/yr)	160 - 320
Incidence of allergic disorders (cases/yr)	100 - 130
Alpha-amylase	
Number of workers in the Netherlands	32,000
Prevalence of sensitisation (cases)	650 - 5,000
Prevalence of allergic disorders (cases)	950 - 1,700

Annex **E**

Abbreviations

Organisations

ARIA	Allergic Rhinitis and its Impact on Asthma
EAACI	European Academy of Allergology and Clinical Immunology
ICD	International Classification of Diseases
ICPC	International Classification of Primary Care
NHG	*Nederlandse Huisartsen Genootschap* [Dutch College of General Practitioners]
NVAB	*Nederlandse Vereniging voor Arbeids- en Bedrijfsgeneeskunde* [Branch organisation for company doctors]
NCvB	*Nederlands Centrum voor Beroepsziekten* [Netherlands Center for Occupational Diseases]
RIVM	*Rijksinstituut voor Volksgezondheid en Milieu* [National Institute of Public Health and the Environment]
SCOEL	Scientific Committee on Occupational Exposure Limits (EU)
WAO	World Allergy Organization
WHO	World Health Organization

Miscellaneous

ALARA	As Low As Reasonable Achievable
BMD	benchmark-dosis
CI	confidence interval
HMM	high molecular weight allergens
SPT	skin prick test
IgE	Immunoglobulin E
IgG	Immunoglobulin G
LLNA	Local Lymph Node Assay
LMW	low molecular weight allergens
NOAEL	no-observed-adverse-effect-level
OEL	Occupational Exposure Limit