Asthma, allergy and environmental factors

Gezondheidsraad **President**
Health Council of the Netherlands

To the Minister of Housing, Spatial Planning
and the Environment

Subject: Report on *'Asthma, allergy and environmental factors'*
Your ref.: DGM/SAS/2004009787
Our ref.: I-309/MD/IV/570-R
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Date: 7 June 2007

Dear Minister,

As requested by State Secretary Van Geel in letter DGMM/SAS/2004009787, I am attaching the Health Council's report *Asthma, allergy and environmental factors*. The report has been prepared by a specially convened Health Council committee, which consulted both the Standing Committee on Health & Environment and the Standing Committee on Infection & Immunity.

The report summarises what is presently known about the role of environmental factors in the development of asthma and allergy. Asthma and allergy are common in the Netherlands. Some of the children born with asthma or allergy have parents with similar disorders, but the majority do not. Environmental factors play an important role in the development of such problems. For example, outdoor air pollution from traffic and other sources can aggravate asthma and other respiratory complaints. Within the home, exposure to cigarette smoke is the principal factor associated with an increased risk of the development or aggravation of asthma in children. The report emphasises that a combination of environmental control measures offers the best prospects for reducing asthma and allergy. In some cases, it is possible to prevent the development of asthma and allergy altogether. To this end, parents are well advised not to smoke during and following pregnancy and to exclusively breastfeed babies for at least three to four months. As with other age groups, combined intervention strategies appear to offer the greatest scope for controlling asthma and allergy in young children.

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Greater understanding of asthma and allergy could provide a basis for better-informed policies. A better picture of the prevalence of these disorders could be obtained if municipal health services were to make use of the recently developed and validated questions on asthma and allergy in the context of the Monitor of Young People's Health. With a view to increasing scientific understanding of the role of environmental factors in the development of asthma and allergy, the Committee recommends a combined analysis of data from the various large-scale birth cohort studies currently in progress in the Netherlands and elsewhere. In view of the amount of work presently being done in this field, the Committee recommends reviewing scientific developments and thinking in approximately five years.

A copy of this report has also been sent to the Minister of Health, Welfare and Sport.

Yours sincerely,
(signed)
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Asthma, allergy and environmental factors

to:

the Minister of Housing, Spatial Planning and the Environment

the Minister of Health, Welfare and Sport

No. 2007/15E, The Hague, 7 June 2007

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.

The Health Council of the Netherlands is a member of the European Science Advisory Network for Health (EuSANH), a network of science advisory bodies in Europe.

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INAHTA

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Executive summary

Asthma and allergy are very common disorders, which have major effects on an individual's quality of life. Increases in asthma and allergy were reported during the final decades of the 20th century, particularly among children. This was not restricted to the Netherlands, as other western countries were similarly affected. With reference to this, the State Secretary for the Environment, has requested advice concerning the role of various environmental factors in the development and increase of these disorders. In response to the State Secretary's questions, the President of the Health Council of the Netherlands appointed a committee, which based its advice mostly on existing reviews of the relevant literature.

Definition of concepts

Asthma is a chronic disorder that is characterised by recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night or in the early morning. These symptoms are usually associated with airway responsiveness to stimuli, variable airflow limitation, and chronic inflammation of the airways. It is not always easy to diagnose asthma, partly due to the episodic nature of this disorder. Asthma can be categorised into allergic and non-allergic forms. These forms differ in terms of the mechanisms which give rise to them, and to some extent they require different preventive measures.

The type of allergy addressed by this advisory report is a hypersensitivity reaction that is based on the production of specific antibodies or immuno-globulins (IgE) in response to certain allergens. The predisposition to produce these antibodies is also referred to as atopy. The presence of a detectable level of IgE antibodies is referred to as sensitisation. The development of allergy symptoms is dependent on an individual's hereditary predisposition, on the intensity and duration of their exposure to allergens, and on the degree of sensitisation involved. Allergic reactions of this kind can manifest themselves in the lungs (allergic asthma), in the eyes and nose (conjunctivitis and allergic rhinitis), or in the skin (atopic eczema). The first two examples are manifesta-tions of an allergy to inhaled substances (aeroallergens), accordingly they are also referred to as respiratory tract allergies.

Asthma and allergy in the Netherlands

The State Secretary's first request to the Health Council was for advice concerning the validity and significance of current data for the prevalence of asthma and other allergic disorders of the respiratory tract in the Netherlands. He specifically wanted details of any changes in these data during recent years, asking the Health Council to assess whether the collection of these data have been sufficiently systematic to allow a conclusion to be reached concerning the actual increase in prevalence over time.

Descriptions of the prevalence of asthma and allergies in the Netherlands can draw on two types of data, one derived from registrations by general practitioners and the other from population studies.

On the basis of five registrations by general practitioners, the number of individuals with asthma in the Netherlands in 2003 was estimated at almost 520,000. The prevalence was 30 per 1,000 men and 35 per 1,000 women. Four to seven percent of primary school children exhibit symptoms of asthma. This means that asthma is currently the most common chronic illness among children in the Netherlands. Asthma, allergic rhinitis, and atopic eczema often occur in the same individual. Follow-up studies have shown that well over half of these children continue to suffer from these symptoms into adulthood. A Dutch study showed that about one in five adults exhibits a hypersensitive response to exposure to stimuli administered via the respiratory tract. One in every three adults has detectable levels of specific antibodies to commonly occurring aeroallergens. These are derived from house dust mites, pets, pollen and moulds.

Increases in asthma and respiratory tract allergy were reported during the final decades of the 20th century, both in the Netherlands and elsewhere. In recent years, the percentage of existing cases of the disease (prevalence) has remained the same, and may even be in decline. The Committee partly attributes the observed changes over time to changes in diagnosis. However, as diagnostic changes in various countries are unlikely to have taken place simultaneously, it mainly attributes the changes in prevalence to genuine changes in the percentage of new cases of the disease (incidence). The Committee advocates the use of the same diagnostic criteria in consecutive future studies, to facilitate the comparison of results. This approach will allow well-founded statements to be made about trends over time.

Monitoring of asthma and allergy

Secondly, the State Secretary asked the Health Council to investigate the nature and size of groups at risk of developing asthma and respiratory tract allergy. He asked the Council whether current monitoring programmes into the geographical and temporal occurrence of these disorders are suitable for monitoring their prevalence in high-risk groups.

The children of asthmatic or allergic parents form a high-risk group for the development of asthma and allergies. Another high-risk group consists of children who were either born prematurely or who had a low birth weight.

The monitoring of asthma and allergy can be described as the periodical measurement, analysis and interpretation of specific indicators of asthma and allergy. Individually, the current monitoring programmes provide too little information about changes in the prevalence of asthma and allergy in the population of the Netherlands. With some modifications, the Local and National Monitor of Young People's Health, which is run by the Dutch Association of Municipal Health Services (GGD Nederland), the National Institute of Public Health and the Environment (RIVM), TNO Quality of Life, and an organisation of care entrepreneurs (ActiZ) could definitely yield insights into changes over time in children. It could also provide opportunities for early diagnosis and treatment. The majority of children with asthma have parents who do not suffer from asthma or allergy. The Committee therefore takes the view that it would be more useful to monitor asthma and allergy in the juvenile population as a whole than to monitor specific high-risk groups separately.

The role of predisposition and environment

Thirdly, the State Secretary asked the Health Council for details of the current level of knowledge concerning the role of – and interactions between – various genetic and environmental factors in the development and increase in asthma and respiratory tract allergy. He also asked the Council to focus specifically on the gaps of knowledge in this field.

Predisposition. Asthma and allergy have long been known to have a hereditary component. The children of asthmatic or allergic parents are at greater risk than other children of developing allergy or asthma. No single gene is responsible for this, instead a series of genes is involved. Regarding the fact that the genetic makeup of the population changes only gradually, any changes in prevalence – beside changes in diagnosis – can be largely attributed to changes in environmental and lifestyle factors.

Environment. Since the 1990s, various studies have been initiated into the role of environmental factors in the development of asthma and allergy in children. The factors that have been investigated include infections, non-infectious microbiological components, allergens, breast feeding, dietary habits, overweight, premature birth, and air pollution inside and outside the home. To date, that research has led to the following conclusions.

Microorganisms. The effect of microorganisms on the development of asthma or allergy varies from species to species. Some studies have suggested that certain gastrointestinal infections reduce the risk of sensitisation. The intestinal flora may have a role to play in this. Conversely, other gastrointestinal infections tend to increase the risk of sensitisation. Little is known concerning the effect of respiratory tract infections on the development of allergic disorders. However, there is strong evidence to suggest that children who developed a respiratory tract infection caused by Respiratory Syncytial Virus (RSV) at an early age are at greater risk of developing asthma later in life. There is no indication of a causal relationship between vaccinations or the use of antibiotics at an early age, and the development of asthma or allergy.

Microbiological components. The relationship between exposure to non-infectious microbiological components in house dust (particularly to bacterial endotoxins) and the development of asthma and allergy is a complex one. While there are indications that endotoxins inhibit allergic sensitisation, there is also evidence pointing to a link between these compounds and the development and aggravation of asthma. It is unclear whether the endotoxins themselves play a

purely causal role here, or whether they serve as an indirect measure of exposure to other environmental factors, such as certain components of moulds. Recent research has identified major interactions with specific genes, which suggests that the relationship between endotoxins on the one hand and asthma and allergy on the other may differ markedly between individuals with different hereditary predispositions.

Allergens. The development of an allergy is always associated with exposure to specific allergens. Follow-up studies on newborns, in which actual measurements were made of their exposure to allergens during the early stages of life, have shown that exposure to allergens from house dust mites and cats in particular increases the risk of developing sensitisation. While sensitisation and asthma are linked, the effect of early exposure to allergens on the development of asthma is not yet fully understood. For the moment, there is little evidence to suggest that allergens shed by pests are of any significance. There is also a lack of clarity concerning the extent to which sensitisation to mould allergens contri-butes to the development of respiratory disorders. However, it is likely that infants with an allergy to cow's milk allergens or chicken protein allergens will be at greater risk of other allergenic disorders when they reach primary school age.

Breastfeeding. Well-designed follow-up studies show that children who have been exclusively breastfed for at least three to four months are less prone to asthma and allergy. This particularly applies to the children of asthmatic or allergic parents. Various studies into the effect of breastfeeding on the develop-ment of asthma and allergy over the long term have yielded ambiguous results.

Dietary habits. Dietary habits also play a part in the development of asthma and allergy. For instance, there is evidence that dietary components in fruit, vegetables and oily fish may have a protective effect. Conversely, vegetable fats and salt have been reported to have harmful effects.

Overweight. Some researchers take the view that overweight increases the risk of developing asthma. However, the relationship is complex in nature, and there is insufficient evidence of a causal association.

Premature birth. Premature birth involves an increased risk of asthma symptoms and pulmonary function disorders in adulthood, but not of allergy. The mechanisms which give rise to respiratory tract symptoms probably differ from those involved in allergic asthma.

Outdoor air pollution. Asthma symptoms are generally aggravated by exposure to potent stimuli in the respiratory tract. Outdoor air pollution (from traffic or summer smog, for example) can also lead to the aggravation of asthma symptoms and other respiratory complaints. As yet, little is known concerning the

extent to which long-term exposure to air pollution is also involved in the development of asthma and allergy.

Indoor air pollution. The major source of indoor air pollution is tobacco smoke. The 2003 Health Council advisory report entitled *The impact of passive smoking on public health* concluded that children whose parents smoke have an increased risk of developing asthma later in life. This is especially true if their mothers smoked during and after pregnancy. In the intervening years, none of the material published in this field has given cause to amend this report's conclusions. Various studies have also revealed a relationship between living in a damp house and the risk of developing asthma or allergy. It is still not completely clear whether increased levels of damp in the home is an indirect measure of exposure to mite or mould products, or whether other factors present in the indoor air might be responsible for the observed effects.

The Committee concludes that hereditary predisposition in particular, together with exposure to specific allergens, plays a role in the development of asthma and allergy. Some microorganisms (or components thereof) may have a protective effect. Premature birth and exposure to air pollution (including tobacco smoke) are probably involved in the development and aggravation of non-allergic asthma. Nothing is known concerning the relative quantitative importance of the various risk factors in terms of the development of asthma and allergy, nor of changes in prevalence over time.

Measures for the living environment

The State Secretary's final question concerned preventive environmental measures. He asked which would be most effective (with reference to specific high-risk groups and phases of life), both in preventing the development of asthma and other respiratory tract allergies and in improving the condition of patients with asthma and respiratory tract allergies by reducing their symptoms.

In addressing this question, the Committee has focused on intervention studies in which the effect of measures to reduce exposure to environmental factors is experimentally investigated.

Amelioration of asthma or allergy symptoms. First the effect of measures to alleviate existing symptoms were evaluated.

House dust mites. Studies carried out in the Netherlands and elsewhere have shown that mattress covers that are impermeable to house dust mite allergens are limited effective in reducing the exposure of asthma and allergy patients to house

dust mite allergen. However, this seldom produced any improvement in the health status of adult asthma and rhinitis patients.

Pets. The most obvious way to reduce pet allergens is to dispose of the pet to which the patient is allergic. However, few intervention studies have explored the efficacy of this measure, possibly because studies of this kind cannot be blinded. Special air filters cannot be recommended, given the inconclusive nature of the results obtained by the few studies that have been carried out with such devices. Nor has any systematic research been carried out into the effect of regularly washing the pet in question in order to reduce the subject's exposure to allergen, or of excluding the pet from the bedroom or living room.

Hypoallergenic food. Mothers who consume hypoallergenic food throughout the period in which they are giving breastfeeding, may, as a result, reduce the severity of any atopic eczema suffered by their child. Further research is needed in this area.

'Healthy' house. A Dutch survey has shown that mattress material in mechanically ventilated homes contains statistically less house dust mite allergen than in naturally ventilated homes. The results of some small-scale intervention studies in Denmark and Finland suggest that asthma symptoms can be alleviated if the individual in question moves to a 'healthy' house, with such amenities as a balanced ventilation system. It is impossible to use blinding in this type of study. For this reason, and because the numerous changes involved in moving house cannot be individually evaluated, the significance of these studies is too limited to allow any recommendations to be made.

Combinations of interventions. The Committee concludes that, to date, interventions in asthma and allergy patients aimed at a single specific environmental factor or a single specific environmental measure, have been found to have a marginally clinical effect. Nevertheless, on the basis of the results of previous studies into substantial allergen avoidance, it is convinced that wide-ranging environmental interventions are indeed effective. Asthma, in particular, is a disorder that is determined by many factors. The associated disease burden can probably only be limited using combinations of interventions involving a range of environmental factors. In everyday practice, however, this is difficult to achieve and to study. In particular, the results of the US Inner-City Asthma Study, involving multiple interventions targeted at individual patients, support the view that tailored interventions and targeted behavioural support can indeed be useful. The Committee advocates further research in this area.

Preventing the development of asthma or allergy. During the past few years, research has also been carried out into the efficacy of environmental measures in preventing the development of asthma or allergy.

House dust mites and pets. The restriction of exposure to allergens produced by house dust mites and pets before birth and during the first year of life has been claimed to reduce the risk of children with a predisposition for allergy developing asthma and allergy. However, the results of studies carried out to date are far from unambiguous. One British study suggested that a stringent reduction of allergens can actually boost sensitisation to house dust mites.

Diet during pregnancy and infancy. At the age of eighteen months, children whose mothers consumed only limited quantities of food allergens during pregnancy are at no less risk than other children of developing atopic eczema. It remains to be seen whether excluding food allergens from the diets of infants themselves is of any use in preventing allergic disorders. The same applies to the benefits of using infant formulas containing non-infectious bacteria, such as lactobacilli. It has yet to be satisfactorily demonstrated whether such products, which are referred to as probiotics, actually inhibit the development of asthma and allergy.

Combinations of interventions. The Committee concludes that no interventions targeting a single environmental factor have proved to be sufficiently effective in preventing the development of asthma or allergy. Interventions involving restricted exposure to allergens, tobacco smoke, and specific dietary components may be more effective. This involves combinations of interventions targeting a range of environmental factors.

Recommendations for everyday practice

The Committee trusts that the following recommendations will be of use to healthcare providers in the context of health education on the effect of environmental measures in alleviating the symptoms of asthma and allergy, or in preventing these disorders entirely.

Ameliorating the symptoms of asthma or allergy. The Committee concludes that interventions using only house dust mite impermeable mattress covers and bedding covers, or special air filters, have not been proven to be effective in reducing the symptoms of asthma and allergic rhinitis. Nevertheless, an approach that is tailored to the individual patient, involving the avoidance of those stimuli and allergens to which they are sensitive, continues to be useful. Some American studies have suggested that, for children with asthma, combinations of intensive interventions involving a range of environmental factors, such as the avoidance

of exposure to both allergens and tobacco smoke, through targeted support of occupant behaviour, can indeed be effective in ameliorating asthma symptoms.

Preventing the development of asthma or allergy. Partly in order to prevent the development of asthma and allergy, parents would be well advised not to expose their child to tobacco smoke during and after pregnancy. Exclusive maternal breastfeeding for at least the initial three to four months reduces the infant's risk of developing sensitisation, atopic eczema, and asthma during its first years of life. Although there is some doubt concerning the duration of this beneficial effect in terms of asthma and allergy, the Committee thinks it is important – bearing in mind that breastfeeding has many other benefits – to uphold the recommendation made by the Netherlands Nutrition Centre*, that infants should be exclusively breastfed up to the age of approximately six months. Other interventions which merely target a single specific environmental factor have been found to be only marginally effective. Here too, the combinations of interventions in young children may offer greater scope. However, there is still too little scientific support to justify the formulation of practically useful recommendations at the present time.

Recommendations for the government

There is convincing evidence that air pollution inside and outside the home can adversely affect the course of respiratory disorders, including asthma. For this reason, the reduction of air pollution is a useful preventive measure. Some examples would be the reduction of vehicle emissions and giving consideration to situating schools and dwellings sufficiently far away from busy roads. The Committee concludes that a strong smoking deterrence policy would be particularly effective in preventing the development of asthma and allergy.

Recommendations for research

In order to better understand the prevalence of asthma and allergy in the Netherlands, the Committee advises municipal health services (GGDs) to make use of the recently developed, validated questions on asthma and allergy in the National Monitor of Young People's Health. In order to improve our understanding of the environmental factors behind the development of asthma and allergy, the Committee recommends that birth cohort studies should be continued for as long as possible. There is one activity in particular that the Committee expects to be

* based on the recommendations by the World Health Organization

highly cost-effective, and which it can wholeheartedly recommend. This involves a combined analysis of uniformly collected data from various major birth cohort studies that are currently being conducted in the Netherlands. By extension, it also makes sense for the Dutch data to be pooled and analysed in an international context. In addition, our understanding of the role played by genes in the development of asthma and allergy is improving continually. To determine which genes in interaction with which environmental factors determine whether an individual does or does not develop asthma or allergy, the Committee also advocates the combined analysis of major studies. Given the large number of studies that are currently in progress, and the good standing of Dutch research in international circles, it may soon be possible to provide more soundly based recommendations and advice on practical matters. Accordingly, the Committee recommends that level of knowledge be reviewed again in around five years' time.

Chapter 1

Introduction

Asthma and allergy are common disorders that have a major influence on quality of life.[1,2] They are also substantial contributors to academic and occupational absenteeism and to health care expenditure. In the latter decades of the twentieth century, there was a rise in the prevalence of asthma and allergy, particularly in children, not only in the Netherlands, but also in other western countries.[3-6] Hereditary predisposition plays an important role in the development of asthma and allergy. However, hereditary factors cannot explain the rising prevalence of these disorders, since changes in the genetic makeup of the population are gradual. Increasingly, therefore, the differences that exist between countries with a 'western lifestyle' and other countries in terms of the initial development and subsequent course of asthma are being attributed to environmental and lifestyle factors, possibly in interaction with genetic factors.[7]

1.1 Asthma and allergy in environmental and health policy

In its first preventive policy document, *Langer gezond leven* (*Staying Healthy Longer*), the Ministry of Health, Welfare and Sport identified asthma as one of the six diseases warranting priority action, on account of their seriousness and cost.[8] In the second preventive policy document *Kiezen voor gezond leven* (*Choosing a Healthy Lifestyle*), which covered the period 2007-2010, the further discouragement of smoking was designated one of the five focuses of policy,

partly in response to the Health Council report *Volksgezondheidsschade door passief roken* (*The Impact of Passive Smoking on Public Health*).[9]

With a view to preventing asthmatic complaints, the Action Programme on Health and Environment organised by the Ministry of Housing, Spatial Planning and Environmental Management (VROM) and the Ministry of Health, Welfare and Sport (VWS) calls for greater attention to be given to the quality of the climate in buildings, especially those where children congregate.[10] In addition, the Programme highlighted the need for greater insight into the precise relationship between indoor environmental quality and asthma. The lack of information available at that time concerning the influence of local, traffic-related air pollution on asthmatic and allergic disorders was also underlined. The Action Programme recommended monitoring allergy, asthma and (indoor) environmental parameters over time and evaluating the findings of long-term studies in this field. The intention is that the follow-up to the Action Programme, the proposed National Health and Environment Strategy, should be aligned with the focuses identified in the Ministry of VWS's second preventive policy document.[9]

The EU Strategy on Environment and Health also pays explicit attention to asthma and allergy in children, since these disorders have been increasing in Western Europe and it is suspected that they may be related to western lifestyles or to indoor or outdoor air pollution, possibly involving exposure during pregnancy and breastfeeding.[11] The prevention and monitoring of asthma and allergy – e.g. through the imposition of control measures in the housing sector – is one of the objectives of the community Action Programme.

1.2 State Secretary's request

Prompted partly by the apparently increasing prevalence of asthma and allergy, the State Secretary for Environmental Management asked the Health Council to report on the extent to which the various environmental factors are responsible for the initial development and the growing significance of these disorders (see annex A). The State Secretary asked first whether the available data were sufficiently reliable to be sure that asthma and other allergic respiratory tract disorders were indeed increasing. Second, he wished to know whether it was possible to identify particular high-risk groups and whether the existing monitoring programmes were sufficient to enable these groups to be followed up properly. Third, the State Secretary asked whether there was a need for a review of scientific knowledge regarding the genetic and environmental factors that influence asthma and respiratory allergy. Finally, the Health Council was asked to identify

the preventive measures that could have a beneficial effect on the initial development and subsequent course of these disorders.

1.3 The Committee and its working methods

With a view to answering the State Secretary's request, the President of the Health Council set up a committee (referred to below as 'the Committee'), whose members are listed in annex B. The Committee met a total of eight times. Its draft report was reviewed by the Standing Committee on Health and Environment and the Standing Committee on Infection and Immunity.

In line with the request raised by the State Secretary, the Committee concentrated on examination of the epidemiological literature concerning the roles played by environmental factors in relation to asthma and allergy. The volume of such literature available and the rapid pace of development in this discipline meant that it was not possible for the Committee to undertake its own systematic reviews of the literature in all the different fields. When formulating its response to the State Secretary's request, the Committee therefore relied significantly on existing reviews and meta-analyses. In addition, certain 'key publications' that had appeared in the period up to 2006 were identified through the Committee members; these included prospective cohort studies and clinical trials concerned with the roles of various environmental factors in the prevalence of asthma and allergy. When consulting representative groups in the wider community, the Committee also asked them to indicate what they considered to be the key publications (see annex C). The Committee used its 'expert judgement' to identify the studies that were of the consistency, quality and authority necessary to support conclusions regarding causal associations. In the selection of key publications, the Committee placed particular emphasis on the strength of the study design: intervention and cohort studies were considered to carry the greatest weight, followed by epidemiological studies of other types.[12]

In addition to articles published in the scientific press, the Committee also made use of background reports by other advisory bodies, such as the National Institute of Public Health and the Environment (RIVM), which on behalf of the Ministry of VWS regularly reports on (changes over time in) the prevalence of asthma and on possible means of prevention.

1.4 Demarcation and co-ordination

This report focuses on the physical environmental factors – as associated with chemical, physical and biological agents – that play a role in the initial develop-

ment, control or aggravation of asthma and allergy. Psychological factors, such as stress, are not considered. Nor has the Committee addressed the medicinal treatment of asthma or allergy.

Where the effects of passive smoking are concerned, this report refers back to an earlier Health Council report on this subject published in 2003. Exposure by means of active smoking is considered only in passing and occupational exposure is not addressed at all.

A report on occupational asthma and allergy is currently being prepared for the Minister of Social Affairs and Employment. A separate report is also planned on the climate inside school buildings.

At the request of the Ministry of Health, Welfare and Sport (VWS) and the Ministry of Agriculture, Nature and Food Quality (LNV), the Health Council has recently published a report on exposure to and the effects of food allergens.[13] In view of the overlap between their respective remits, the Committee on Environmental Factors and Asthma and the Food Allergy Committee held one joint meeting in order to facilitate the harmonisation of their investigations. The two committees worked closely together on common development mechanisms and on the terminology of allergic disorders.

Because it has been suggested in some quarters that vaccination may play a role in the development of asthma and allergy, the Committee also exchanged information with the Health Council committees considering the reform and extension of the National Immunisation Programme and adverse responses to vaccinations given in the context of the latter programme. Furthermore, a joint session of the Committee on Environmental Factors and Asthma and the Food Allergy Committee was attended by Professor W. van Eden, who was invited to give his views on the way that vaccination influences the immune system in relation to the development of allergy.

1.5 Structure of this report

After this introduction, the report continues with a brief explanation of certain terminological matters (section 2). Each of the following four sections is devoted to one of the central requests posed by the State Secretary. First, section 3 covers the prevalence of asthma and allergy and the changes in their prevalence over time. Section 4 then identifies a number of high-risk groups and analyses the scope for monitoring. Third, the hereditary and environmental factors influencing the development of these disorders are considered in section 5. Fourth, section 6 looks at ways of preventing asthma and allergy. The report concludes with a section itemising the Committee’s recommendations.

Chapter 2

Terminology

When commissioning this report, the State Secretary referred to ‘asthma and respiratory allergy’ and to ‘primary and tertiary preventive measures’. In this section, the Committee accordingly clarifies what it understands these and other related terms to mean. A glossary is also appended to the report (annex D).

2.1 Asthma

2.1.1 Definition

In 2002, working in conjunction with the European Academy of Allergology and Clinical Immunology, the World Health Organization defined asthma as follows[14-15]:

‘Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells, eosinophils and T-lymphocytes. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. This inflammation also causes an associated increase in airway responsiveness to a variety of stimuli.’

One problem with this definition is that it is not readily applicable in the context of epidemiological surveys or population studies concerned with the incidence of

asthma.[16] The standardised study of subjects selected at random from the general population requires the application of uniform diagnostic criteria (see 2.1.3). The most useful epidemiological definition of clinically significant asthma was proposed in the 1990s: wheezing in the last twelve months in combination with respiratory hypersensitivity.[17] In practice, however, the measurement of bronchial hyperreactivity* in large groups of children proves to be time-consuming and therefore expensive. For this reason, asthma in young children is generally defined on a purely anamnestic basis, on the basis of symptoms (physical complaints) or on the basis of a doctor's diagnosis. Most epidemiological surveys of adults work exclusively on the basis of anamnestic data collected from interviews or questionnaires.

2.1.2 *Manifestations*

For the purposes of etiological research, prognosis and prevention, five clinical manifestations of asthma are recognised, which are probably associated with different genotypes.[19,20] Three of the five affect children[19]:

- transitory wheezing in infants
- non-allergic wheezing in toddlers and older pre-school children
- allergic wheezing, often developing at pre-school age.

The other two types of asthma do not develop until adulthood:

- (occupational) asthma associated with exposure to toxic agents
- non-allergic asthma, as seen particularly in postmenopausal women, e.g. in response to oestrogen treatment.[20]

Because of the impact that any preventive measures might have, asthma in children is given particular attention in this report.

2.1.3 *Diagnostic criteria*

According to the standard applied by the Netherlands Association of General Practitioners (NHG), the symptoms of asthma in children up to four years old consist of recurrent coughing, wheezing or 'feeling congested'.[21] From the age of four, wheezing and breathlessness are the chief symptoms. The NHG guidelines

* Bronchial hyperreactivity or respiratory hypersensitivity (epidemiological definition): a reduction in the forced exhalation volume per second (FEV1) of at least 15 to 20 per cent following provocation with a hypertonic saline solution or methacholine or histamine[18]

on the diagnosis of asthma in adults refer to patients who are periodically affected by breathlessness or wheezing, sometimes associated with (productive) coughing, and who are found to benefit from using a bronchodilators.[22]

Partly because of the disease's episodic nature, the anamnestic diagnosis of asthma is not always straightforward.[23] In children, differentiation between asthma and acute viral bronchitis or bronchiolitis can be difficult. Greater diagnostic certainty depends on the combination of physical complaints and a family anamnesis or history of problems with the results of a physical examination.

In childhood, asthma is often accompanied by an allergy to inhalation allergens, i.e. what the State Secretary refers to as 'respiratory allergy'. Additional allergological testing – e.g. for the presence of specific antibodies or immunoglobulins (IgE) in the serum – may therefore be helpful. Such testing is considered in the next section.

2.2 Allergy, sensitisation and atopy

2.2.1 Definitions

The Committee has followed the definitions of 'allergy' and the related terms proposed by the European Academy of Allergology and Clinical Immunology, which were accepted – subject to a minor modification* – by the World Allergy Organization in 2004.[14,24,25]

Allergy is a hypersensitivity reaction initiated by specific immunologic mechanisms.[25] This allergic reaction manifests itself in the increased prevalence of specific immunoglobulins, usually of isotype E (IgE). Such an allergy is therefore often described as an IgE-mediated allergy or a type I allergic reaction. An allergic reaction of this type involves the specific recognition of a particular allergen**. In the event of repeated exposure to the allergen in question, the level of specific IgE increases and clinically observable allergic symptoms may develop. This report is concerned only with allergies of the type described.

The Committee defines sensitisation as the presence of allergen-specific IgE antibodies in the body, regardless of whether the person has actually developed allergic symptoms. The presence of such antibodies can be discerned by means of either a skin prick test or a blood test.

Atopy is defined by the Committee as a tendency to produce IgE antibodies in response to exposure to allergens. An atopic constitution is a hereditary predis-

* The phrase 'atopic eczema dermatitis syndrome' was replaced in 2004 by 'dermatitis and eczema'.
** Allergens: xenobiotic, non-infectious agents.

position to IgE-mediated allergic disorders (known also as ‘atopic’ disorders), such as allergic asthma, allergic rhinitis and atopic eczema. Each manifestation – phenotype – of the atopy is associated with a different gene.[26]

2.2.2 *Manifestations*

An allergic reaction may manifest itself in the lungs (allergic asthma), in the nose and eyes (allergic rhinitis and conjunctivitis) or on the skin (atopic or constitutional eczema). Whether an allergen triggers symptoms depends on a patient’s hereditary predisposition, the intensity and duration of his/her exposure and the degree of prior sensitisation.

2.2.3 *Diagnostic criteria*

Allergic rhinitis is an IgE-mediated hypersensitivity reaction of the nasal mucous membranes, which – according to the guidelines of the Netherlands Association of General Practitioners (NHG) – takes the form of a more than four weeks lasting or frequently recurring disorder, characterised by nasal congestion, a running nose, sneezing or nasal itching, which occur in response to exposure to inhalation allergens.[27,28] Distinction is often made between seasonal allergic rhinitis or hay fever, which is triggered by pollen from trees or grasses, and non-seasonal allergic rhinitis, which is triggered by allergens from house dust mites or pet animals.

Atopic eczema is a pruritic skin disorder involving erythema, inflamed pimples, blisters, scabs, skin flaking or lichenification and at least three of the following symptoms[29]:

- typical localisation, depending on age:
  - in children less than two years old: face, scalp, outer surfaces of the extremities and trunk
  - in adults and children more than two years old: inner surfaces of the extremities
- development of allergy in childhood
- chronic recidivist course
- personal or family anamnesis with atopic syndrome (asthma, allergic rhinitis or conjunctivitis, atopic eczema).

2.3 Prevention

Before addressing the State Secretary’s request about the most effective ways of preventing asthma and allergy, it is important to distinguish between primary,

secondary and tertiary prevention. Primary prevention entails preventing new cases of an illness – in the broadest sense of the word – by removing its cause or causes.[30] In the context of this report, the Committee has interpreted this as implying prevention of the first signs of asthma or allergy. Secondary prevention is the detection and treatment of illness before the 'patient' is aware of having it.[30] Where asthma or allergy is concerned, this might involve testing a person for bronchial hyperresponsiveness or sensitisation, before he or she has developed any asthmatic or allergic disorders. Tertiary prevention involves preventing the manifestation or aggravation of an illness that the patient already has.[30] In an asthma or allergy case, tertiary prevention might therefore mean controlling the manifestation of symptoms by, for example, avoiding contact with the stimuli or allergens that trigger attacks. In this report, the Committee focuses primarily on the effectiveness of primary and tertiary preventive measures as means of preventing, respectively, the initial development and the aggravation of asthma and allergy. Nevertheless, in section 4, the Committee briefly considers the early detection (i.e. secondary prevention) of asthma or allergy symptoms.

Chapter 3

Asthma and allergy in the Netherlands

The State Secretary's first request was as follows:

Can the Health Council comment on the validity and significance of the data available concerning the prevalence of asthma and other allergic respiratory tract disorders in the Netherlands and concerning the changes in the prevalence of these disorders in recent decades? Was the collection of the data in question sufficiently systematic that one may conclude that the prevalence of these disorders has actually risen over time?

The Committee's answer to this request is based largely on two RIVM reports, published in 2000 and 2002, concerning asthma-related morbidity.[18,31] Since publication, some of the reported data have been updated and additional data have been added concerning allergic rhinitis and atopic eczema.

The data available concerning the incidence and prevalence of asthma and allergy in the Netherlands fall into two categories: data from epidemiological studies focusing specifically on these disorders and data from established morbidity and mortality registers.[18] The richest source of information of the second kind is general practice data registration systems. Hospital registers and mortality registers are less revealing, since asthma and allergy lead to relatively few hospital admissions or deaths. Such registers are, however, a valuable source of information about the seriousness of asthma and allergy.

This section begins with an assessment of the reliability of the data available in the Netherlands. This is followed by a summary of what may be concluded regarding the incidence and prevalence of asthma and allergy in the Netherlands. In the context of this summary, distinction is made wherever possible between sensitisation, complaints and disorders. The final subsection is devoted to the question of whether asthma and allergy have indeed become more prevalent in the Netherlands over the last few decades.

3.1 Reliability of the Dutch data

The reliability of incidence and prevalence data* is determined by the validity of the diagnosis and by the completeness and representativeness of the recorded data.[18] Where these determinants are concerned, epidemiological surveys and general practice data registration systems each have their own distinct strengths and weaknesses.

3.1.1 Epidemiological surveys

As indicated in section 2, epidemiological surveys designed to shed light on the frequency of these disorders by collecting data from a group of subjects representative of the general population in accordance with a standardised model are not based upon the clinical diagnosis of asthma or allergy.[18] Large-scale surveys typically look at the prevalence of various self-reported, specific asthma symptoms, such as attacks of wheezing, chest constriction or breathlessness.

Validity of the diagnosis

Epidemiological surveys should ideally make use of uniform definitions of asthma or allergy. It is only by using the same terminology, the same questionnaires with clear symptom definitions and the same objective characteristics that the findings from different studies or concerning different populations can be meaningfully compared. Objective symptoms of asthma or allergy include: functional lung disorders, bronchial hyperresponsiveness or positive skin tests.

Completeness

Prevalence data collected in an epidemiological survey can be distorted by selective participation (selection bias). On the other hand, there is less risk than there

* - Incidence: number of new cases, typically per thousand individuals, over a particular period
- Prevalence: overall number of cases, typically per thousand individuals, over a particular period

is with data from general practice data registration systems of distortion due to under or over-registration resulting from differences in the study populations' inclination to seek assistance.

Representativeness

Most of the epidemiological studies were performed in particular regions of the Netherlands and it cannot therefore be assumed that the results are valid for the Dutch population as a whole. This was not the case, however, with the cross-sectional study that took place in 1992, which involved 135 primary schools in fifteen regions. This representative national survey[32] revealed no major geographical differences in the prevalence of asthma symptoms. No subsequent study has sought to gather data on a nationwide basis.

3.1.2 General practice data registration systems

Validity of the diagnosis

In principle, all general practice data registration systems should be consistent with international standardised diagnostic criteria (ICPC*). However, a general practitioner's diagnosis is a working diagnosis, which is not always objectivised by further testing and not always updated in the records if it subsequently proves to be incorrect. When a general practitioner (GP) diagnoses 'asthma', this may not reflect the results of objective lung function testing, and the GP may not correct his or her records if the diagnosis is brought into question by the ineffectiveness of the trial treatment. This can result in the over-diagnosis of asthma. Alternatively, some of the symptoms of asthma – such as coughing, breathlessness, acute bronchitis, upper or lower respiratory tract illnesses – are liable to be recorded as disorders in their own right, under their own ICPC codes. Where this happens and no asthma diagnosis is made, under-reporting can occur.

Completeness

Differences in GPs' diagnostic practices can lead to differences in the degree of over or under-recording of asthma or allergy cases.[18] Over or under-recording can also result from differences in patients' inclination to seek help.[33] Not everyone who has asthma symptoms consults his or her GP, so that the recorded data usually understate the number of people who suffer from the disease.[34,35] Allergic rhinitis is often under-diagnosed as well.[36]

* ICPC: International Classification of Primary Care (WHO).

Representativeness

The Dutch National Study of General Practice gathers data from a representative sample of GP-practices across the whole country.[37] However, all the other general practice data registration systems, including the long-running Continuous Morbidity Registration (CMR) programme operated by university primary care practices in the town of Nijmegen, are confined to certain regions. Since earlier epidemiological studies have found no major geographical differences in the prevalence of asthma symptoms, it is reasonable to suppose that estimates based on information from the Netherlands' general practice data registration systems do reflect the actual prevalence of diagnosed asthma.

Taking all factors into account, general practice data registration systems are valuable mainly for tracking changes over time. Their importance in this context is heightened by the fact that the number of Dutch epidemiological studies that have been repeated is too small to support firm conclusions.[1]

3.2 Prevalence and incidence data

In recent decades, it has been reported in various publications that asthma and allergy are very common, especially among children in western countries.[38-40] Both disorders are much less prevalent in Eastern and Southern Europe.[41] Internationally, the Netherlands is about midway up the prevalence 'league table' for these disorders.[38] The data concerning asthma and allergy in the Netherlands are considered in more detail in this section.

3.2.1 Asthma

On the basis of data from five general practice data registration systems, the number of people with asthma in the Netherlands in 2003 was estimated to be 519,800: 29.5 per thousand men and 34.5 per thousand women.[42] In childhood, males are more likely to suffer from asthma than females, but in adulthood the position is reversed (see figure 1).

The number of new asthma cases occurring in 2003 was estimated at 117,300: 6.5 per thousand men and 7.9 per thousand women.[42] The ratio between incidence and prevalence (one to four or one to five) illustrates that asthma need not be a lifelong disease. The low ratio between the prevalence of asthma in adults and its prevalence in children indicates that not all asthmatic children continue to experience problems in adulthood. This has been confirmed by studies into the

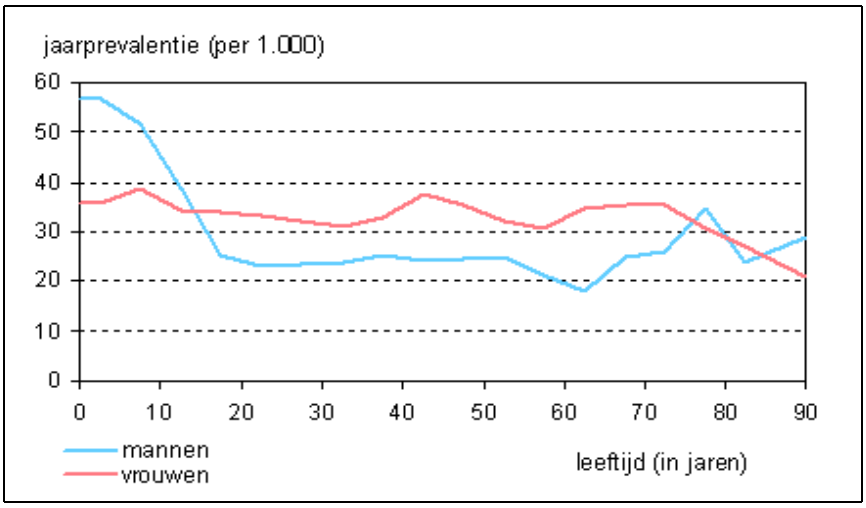

Figure 1 Annual prevalence of asthma by age and gender in 2003, as deduced from five general practice data registration systems.[42]

course of asthma in children and the associated prognosis; nearly half of asthmatic children were found to have no asthma problems later in life.[43] However, more than half continued to be troubled by the disease as adults.

Asthma in children

General practice data indicate that asthma is most prevalent in children between five and nine years old. In this age group, sixty-one out of every thousand boys and forty out of every thousand girls presented to their GPs with asthma in 2003.[42] Various representative studies support the conclusion that between 4 and 7 per cent of primary school children have asthma at any given point in time (table 1).[37,44,45] Hence, asthma is now the most common chronic illness among children in the Netherlands.

Asthma in adults

The most significant epidemiological studies of adult asthma in the general population conducted to date have been the European respiratory studies of the Netherlands (ELON) in 1992 and 2002 and the project 'Monitoring of Risk Factors and Health in the Netherlands' (MORGEN) conducted in the mid-nineties. Among all surveyed adults in the 1990s, the prevalence of asthma symptoms, such as breathlessness and wheezing, was 14 to 18 per cent and 3 to 5 per cent reported having at some time had asthma.[31]

Table 1 Prevalence of asthma in children, as indicated by various types of study.[46]

	Study	Number of subjects	Age	Study period	Prevalence (%)
Presenting to GP with asthma[a]	GP data	25 762	0- 4	2000-2002	5.4
		24 539	5- 9		4.3
		24 093	10-14		3.3
Reported asthma diagnosis[b]	PIAMA	3 170	0- 1	1997-1998	5.7
		3 170	1- 2	1998-1999	4.4
		3 170	2- 3	1999-2000	4.1
		3 170	3- 4	2000-2001	4.1
		3 170	4- 5	2001-2002	3.9
Wheezing and bronchial hyperresponsiveness[c]	ISAAC-II	1 098	7-12	1997-1998	7.2

[a] Number of people presenting to their GP at least once with asthma (as diagnosed by the GP) in the course of a given year, as a percentage of the entire practice population.

[b] Parents of children (number for whom complete records were available: 3,170) monitored for the first five years of life, who answered 'Yes' to both of the following two questions: 'Has a doctor ever diagnosed asthma in your child?' and 'Has your child had asthma at all in the last twelve months?

[c] Wheezing in the last twelve months (reported) and bronchial hyperresponsiveness (measured).[45]

Sources: the Second Dutch National Study of General Practice, the PIAMA study* and the Dutch section of the ISAAC II report**.

Disease burden

On average, asthma claims approaching a hundred lives a year in the Netherlands: almost forty men and fifty women.[47] Because the individuals concerned are typically quite young, this implies a high number of lost life-years per fatality. The total number of lost life-years associated with these deaths is about 950 in men and 800 in women. Asthma is also responsible for considerable quality-of-life impairment, with an annual 30,000 to 100,000 lost Disability Adjusted Life Years (DALYs***). The Committee believes that this level of disease burden is sufficient to justify prioritising asthma in the Ministry of VWS's prevention policy.

* PIAMA: Prevention and Incidence of Asthma and Mite Allergy.

** ISAAC: International Study of Asthma and Allergy in Children.

*** In a DALY calculation, the number of people with a given condition is multiplied by the length of time that they have the condition (or the length of time by which their lives are shortened) and a factor equating to the seriousness of the condition (on a scale where 0 represents perfect health 1 represents death; the weighting factor for serious asthma is 0.36).[48]

3.2.2 *Bronchial hyperresponsiveness*

Some people are hypersensitive to specific stimuli; they exhibit objectively reproducible symptoms and phenomena when exposed to the stimuli in question in dosages that most people can tolerate.[24] One indicator of respiratory hypersensitivity is the bronchial hyperresponsiveness. The 1992 ELON study demonstrated that older adults (forty-five to seventy years old) were statistically more likely to have a sensitised respiratory tract than younger adults (twenty to forty-five years old) – the relevant prevalence figures being 23 per cent and 17 per cent.[49] In the 2002 re-run of the ELON study, 22 per cent of people in the twenty to forty-five-year-old age group exhibited bronchial hyperresponsiveness in a given year. No data were published regarding older people.

3.2.3 *Sensitisation to inhalation allergens*

In the 1992 ELON study, 32 per cent of the 2,496 tested adults were found to be carrying specific IgE against one or more of the five studied inhalation allergens.[50] In twenty to thirty-year-olds, the figure was 46 per cent. Some 427 people from this last group underwent specific allergy tests; about a third of them were found to have IgE against house dust mites. The corresponding figure for sixty to seventy-year-olds (n=515) was less than 15 per cent. No similar studies have since been conducted in the Netherlands.

3.2.4 *Allergic rhinitis*

In the Dutch part of the ISAAC II study*, which involved primary school children between seven and twelve years old surveyed in 1997/1998, 23.1 per cent of subjects reported having suffered nasal problems at some time and 18.5 per cent having suffered nasal problems in the last year.[51] In this study, the questions were addressed to the parents.

In the 1992 ELON study, whose subjects were adults, 28 per cent of the twenty to twenty-five-year-olds and 18 per cent of the sixty-five to seventy-year-olds reported suffering from a ‘nasal allergy’.[49] The question that subjects were asked was: ‘Do you suffer from any form of nasal allergy, such as hay fever (no/yes)?’ In 2002, 33 per cent of subjects aged between twenty and forty-five reported having such problems.

* ISAAC: International Study of Asthma and Allergy in Children.

In 2001, the Second Dutch National Study of General Practice put the incidence of 'hay fever/allergic rhinitis' at 8.8 new cases per thousand individuals per year and the annual prevalence at 27.8 cases per thousand individuals: 25.0 among men and 30.7 among women.[37] Where children under the age of eighteen were concerned, an incidence of 9.9 was reported.

Also in 2001, the Continuous Morbidity Registration (CMR) programme in Nijmegen indicated that the annual incidence of seasonal allergic rhinitis* (hay fever) was four new cases per thousand men and nine per thousand women.[52] Information about non-seasonal allergic rhinitis is not separately recorded within the programme.

Disease burden

Although allergic rhinitis is not associated with serious morbidity or mortality, this disorder does have quality-of-life implications. Studies carried out in other countries indicate that allergic rhinitis affects patients' physical, social and emotional function.[53] Allergic rhinitis has a negative influence on children's learning ability, for example, and on adults' quality of life.[54,55] Hence, allergic rhinitis has implications for academic performance and occupational productivity.[56]

Association between asthma and allergic rhinitis

Allergic rhinitis is a strong, independent risk factor for the development of asthma.[57-59] Conversely, 80 to 90 per cent of asthma patients also suffer from allergic rhinitis.[60,61] Allergic rhinitis in children with asthma is associated with additional expenditure on medication, additional GP consultations and additional and longer periods of asthma-related hospitalisation.[62,63] The international ARIA classification system**, which was introduced in 2005 and has been incorporated into the revised NHG standard on rhinitis, emphasises the association between asthma and rhinitis.[64] Distinction is made between intermittent and persistent rhinitis. Especially patients with the persistent form of allergic rhinitis should be checked for asthma.

3.2.5 Atopic eczema

It is difficult to diagnose atopic eczema in the context of questionnaire-based epidemiological studies, since there is no definite diagnostic criterion that one can

* In the CMR programme, there is no separate code for all forms of allergic rhinitis: non-seasonal allergic rhinitis has the same code as hyperreactive (non-allergic) rhinitis.

** ARIA: Allergic Rhinitis and its Impact on Asthma.

apply (see 2.2.3). The prevalence data for children and adults presented below should therefore be regarded as merely indicative of the prevalence of skin allergy or skin rash.

In the Dutch part of the ISAAC II study*, which involved primary school children between seven and twelve years old surveyed in 1997/1998, 17.7 per cent of subjects reported having had skin rash at some time and 13.1 per cent having had skin rash in the last year.[51]

In the 1992 ELON study of adults, 36 per cent of the twenty to twenty-five-year-olds and 30 per cent of the forty-five to seventy-year-olds reported suffering from skin allergy or eczema.[49] Subjects were asked the following question: 'Have you ever had eczema or a form of skin allergy (no/yes)?' Women were demonstrably more likely to report suffering skin allergies or eczema than men. No more recent data are available.

Annual prevalence and incidence data for atopic eczema, as calculated by the RIVM from data obtained through the National General Practice Information Network (LINH) for the purpose of the National Public Health Compass, are presented in table 2.[65] The annual prevalence in 2003 was between fifteen and seventeen cases per thousand individuals (1 to 2 per cent).

Table 2 Annual prevalence (per thousand individuals and absolute) and annual incidence (per thousand and absolute) of atopic eczema (cases) known to general practitioners in 2003; data are age-standardised to the population of the Netherlands in 2003.[65]

Compass estimate for 2003	Annual prevalence men	Annual prevalence women	Incidence men	Incidence women
Per thousand individuals	15.21	16.82	5.53	6.25
Absolute	122 164	137 861	44 396	51 249

Source: General practice data registration systems; the average estimated incidence in 2003 is based on NIVEL's** National General Practice Information Network (LINH).

Disease burden

In the Dutch population as a whole, the calculated quality-of-life impairment attributable to atopic eczema is between 10,000 to 30,000 DALYs.[47]

Association between asthma, rhinitis and eczema

Little recent information is available concerning the numbers of people suffering from the combination of atopic eczema, asthma and rhinitis. However, studies

* ISAAC: International Study of Asthma and Allergy in Children.
** NIVEL: Netherlands Institute for Primary Health Care Research.

conducted elsewhere indicate that a third of patients with atopic eczema also suffer from asthma.[66,67]

Table 3 Annual percentage prevalences of wheezing and allergic nasal and skin disorders in twelve to fourteen-year-olds in the Netherlands in 2003.

	Men	Women
Wheezing	11.0	13.5
Rhinitis	24.5	31.9
Pruritic skin rash	10.1	16.8

Source: Questionnaire-based study following the ISAAC protocol.[69]

Dutch investigators have put the proportion of eczema patients who also suffer from rhinitis at more than 80 per cent.[60] More than four fifths of children with atopic eczema were found to develop allergic rhinitis or asthma later in their youth.[68] Table 3 shows summarised annual prevalence data for wheezing and allergic nasal and skin disorders, as obtained from a Dutch questionnaire-based study of twelve to fourteen-year-olds conducted in 2003.[69]

Table 4 presents summarised annual prevalence data for asthma and (other) allergic disorders derived from the Second Dutch National Study of General Practice.[37]

Table 4 Annual prevalences of asthma and allergy (per thousand individuals) in the Netherlands in 2000/2001.

	Men	Women
Asthma (all ages)	24,7	27,5
Asthma in young children (1-4)	66,4	43,5
Allergic rhinitis	25,0	30,7
Atopic eczema	14,4	17,1

Source: Second Dutch National Study of General Practice.

3.3 Changes over time

3.3.1 Asthma

Some time ago, a rise in the prevalence of various asthma symptoms was reported on the basis of a meta-analysis of data from Dutch epidemiological studies involving primary school children in the period 1985-1995.[3] However, a statistical re-analysis of the same data has shown that only recent breathlessness and asthma diagnosis by a doctor have become more prevalent.[31]

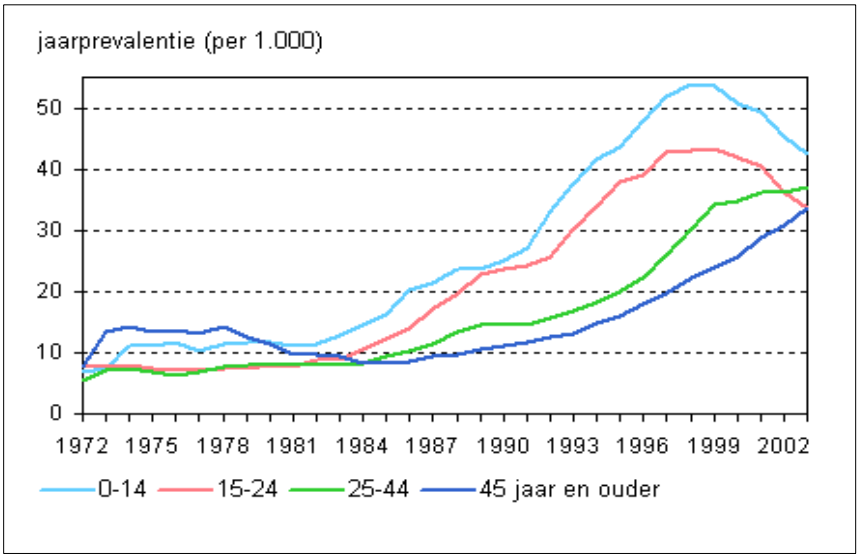

Figure 2 Annual prevalence (per thousand men and per thousand women) of GP-diagnosed asthma in the period 1971 to 2003 (three-year rolling average); age-standardised to the population of the Netherlands in 1990 (Source: CMR Nijmegen).[2,77]

The re-run of the ELON study in 2002 found a statistically significant increase in the prevalence of asthma symptoms (from 17 to 24 per cent) in adults up to the age of forty-five in Groningen since 1992.[70] Adults of forty-five and older were not included in the re-run.

In view of the lower response rate in 2002, and the fact that people with asthma symptoms were more likely to respond than those without, the possibility cannot be excluded that the prevalence of asthma was in fact stable in this period. Other repeated questionnaire-based studies, conducted in the Netherlands (province of Limburg) and beyond, found a stabilisation in the prevalence of asthma symptoms in children since 2000.[71-76]

Information from the longer-running general practice data registration systems (e.g. the Continuous Morbidity Registration (CMR) programme in Nijmegen) indicates that the number of people presenting to their GPs with asthma remained almost constant between 1971 and 1983, but has since risen sharply. The rise has been most marked among children. Whereas the prevalence was just five cases per thousand people in 1983, it had gone up to twenty-five cases per thousand people by 1999.[31] These figures suggest that asthma was one of the diseases

whose recorded prevalence in the Netherlands rose most sharply in the period 1990 to 2000.[47] The most recent, age-specific figures (see figure 2) suggest that since 2000 there has been no further increase – and possibly a decline – in the number of people visiting their GPs because of asthma.[1,2,77] Because these figures are based on a three-year rolling average, no more recent data are available.

The fall in the number of new cases of asthma recorded in the Dutch National Study of General Practice (from 18.8 per thousand person-years in 1987 to 13.3 in 2001) serves as further evidence that the rise in the prevalence of asthma has been halted.[37]

In contrast to the prevalence of asthma in the general population and in general practice, the standardised number of asthma-related hospital admissions has remained constant since the 1990s, after falling in the 1980s.[77,78] There has also been little change in the level of asthma-related mortality, after a sharp fall at the start of the 1990s, particularly among older people. In both cases, the likely cause is better medical treatment of asthma.[79]

3.3.2 *Bronchial hyperresponsiveness*

Comparison of data from the 2002 ELON study with the findings of a similar survey conducted in 1992 indicates that there has been no statistically significant rise in the prevalence of bronchial hyperresponsiveness.[70] In view of the low response rate in 2002 (20 per cent), and the fact that people with asthma symptoms were more likely to respond than those without, the possibility cannot be excluded that the prevalence of bronchial hyperresponsiveness in fact fell in the period 1992-2002.

3.3.3 *Sensitisation to inhalation allergens*

By means of successive serological tests conducted at three points in time, a British study showed that sensitisation was less common in earlier birth cohorts than in later cohorts.[80] This indicates that people are becoming sensitised increasingly early in life. However, no comparable repeated epidemiological surveys have been carried out in the Netherlands. The Committee is not therefore able to identify any patterns of change over time in the sensitisation of different subgroups of the Dutch population, or any such changes in the occurrence of asthma or allergic disorders.

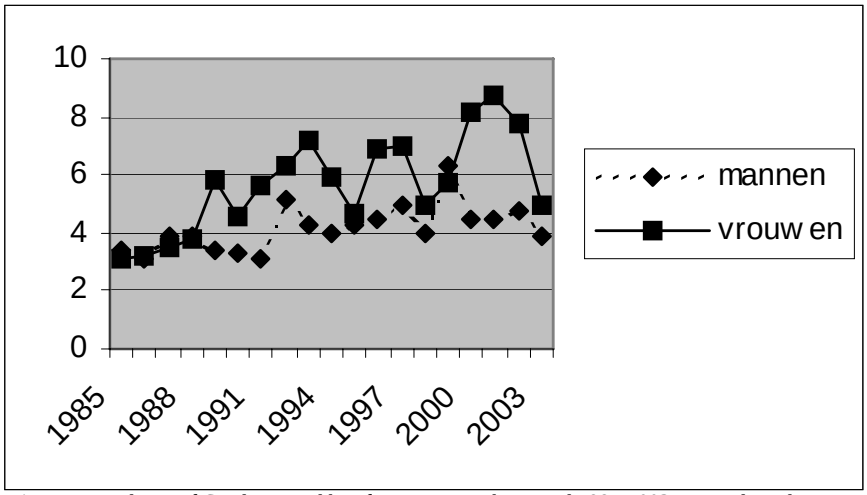

Figure 3 Incidence of GP-diagnosed hay fever cases in the period 1985-2003, age and gender-standardised in accordance with CBS data on the Dutch population in 1994 (Source: CMR Nijmegen).[81]

3.3.4 *Allergic rhinitis*

Comparison of data from the 2002 ELON study with the findings of a similar survey conducted in 1992 indicates that the prevalence of 'nasal allergy' in adults has risen since 1992.[70] It appears that a cohort effect may be at work*: the prevalence of nasal allergy is higher in later birth cohorts.

From the Dutch National Study of General Practice, it is apparent that, among children under the age of eighteen, the annual incidence of hay fever or allergic rhinitis has risen from 6.5 cases per thousand individuals in 1987 to 9.9 per thousand in 2001.[37] The study does not distinguish between seasonal and non-seasonal allergic rhinitis. The prevalence figures obtained from the two national studies are consistent (27.4 cases per thousand individuals in 1987 and 27.8 per thousand in 2001), but it is hard to read much into this, since the populations involved were different.

Nijmegen's Continuous Morbidity Registration (CMR) programme put the annual age-standardised incidence of GP-diagnosed seasonal allergic rhinitis** (hay fever) for 1985 at three new reported cases*** per thousand men and

* Cohort effect: an effect involving historical differences between successive generations.

** In the CMR, the various forms of allergic rhinitis are not classified separately: non-seasonal allergic rhinitis has the same classification code as the hyperreactive (non-allergic) rhinitis.

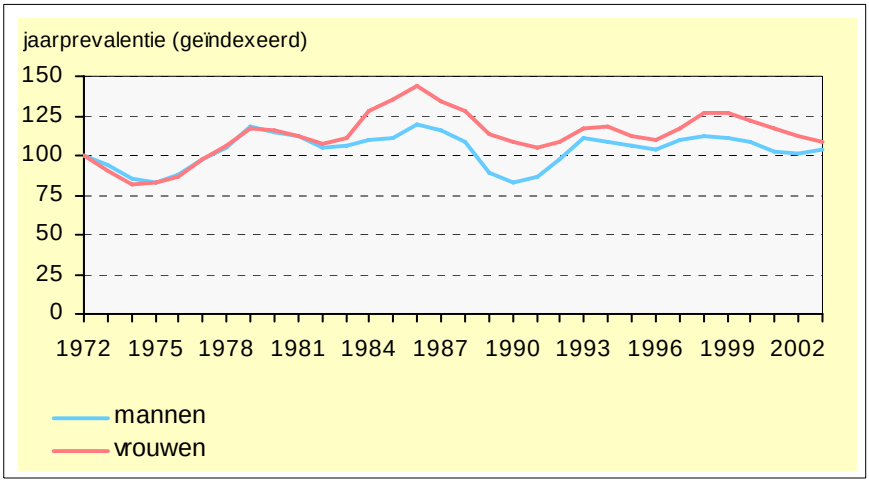

Figure 4 Prevalence of atopic eczema (per thousand individuals) in the period 1971-2003 (three-year rolling average); age-standardised to the population of the Netherlands in 1990 and indexed (1972 = 100) (source: CMR Nijmegen).[65]

women.[52] By 2001, the incidence had risen to four per thousand men and nine per thousand women (see figure 3). Since then, however, the incidence has fallen again. In the CMR, hay fever (seasonal allergic rhinitis) and hyperreactive rhinitis (rhinitis of unknown cause) have been classified separately since 1985; previously, the two disorders came under the same heading.

To sum up, repeated epidemiological studies in Groningen have indicated that the prevalence of allergic rhinitis rose in the period 1992 to 2002. General practice data for the period 1985 to 2001 also show an increase in the incidence of (seasonal) allergic rhinitis. Since then, the incidence appears to have fallen again.

3.3.5 *Atopic eczema*

Changes in the prevalence and incidence of atopic eczema have been tracked since 1971 in the context of the Continuous Morbidity Registration (CMR) programme operated by university primary care practices in the town of Nijmegen.

The prevalence of atopic eczema rose until the mid-1980s, particularly among women (see figure 4).[65,82]

*** not previously reported to the GP

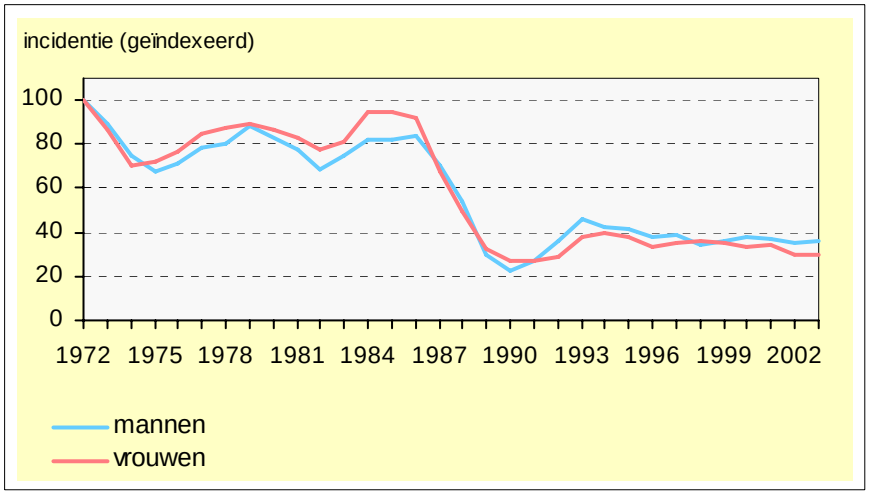

Figure 5 Incidence of atopic eczema in the period 1971-2003 (three-year rolling average); age-standardised to the population of the Netherlands in 1990 and indexed (1972 = 100) (source: CMR-Nijmegen).[65]

The annual incidence remained almost constant for both men and women in the period 1971 to 1986, before falling in the period up to 1990.[65,82] Between 1990 and 2003, there was almost no change in the incidence (see figure 5).

3.4 Explanations for the changes in the prevalence

In order to respond to the second part of the Minister's request – concerning the extent to which the prevalence of asthma and allergy has actually changed – the Committee has grouped the possible explanations for the observations described above under two headings. On the one hand, it may be that the study data merely highlight 'artefacts', i.e. the effects of changes in diagnostic practices or changes in the behaviour or awareness of the public and/or of doctors. On the other hand, the study data may reflect actual epidemiological changes, such as shifts in the population's sensitivity to allergens or exposure to environmental factors. This section of the report is devoted largely to an examination of the artefacts that might have given rise to the apparent rise and more recent stabilisation in the prevalence of asthma and allergy. The role of environmental factors is considered in section 5.

3.4.1 *Apparent rise in the prevalence of asthma and allergy up to the late 1990s*

As indicated in subsection 3.3, asthma, allergic rhinitis and atopic eczema were all reported to be on the increase in the Netherlands in the later decades of the twentieth century. Various possible explanations for these observations are considered in the following paragraphs.

Developments in diagnostic practice

The apparent rise in the prevalence of asthma is almost certainly attributable partly to developments in the field of diagnosis.[2] During the period in question, the medical profession's ability to diagnose the disease improved, diagnostic guidelines were clarified, the taboo surrounding the diagnosis diminished and awareness of the illness increased. It would be very surprising if these developments did not lead to a higher proportion of asthmatics being diagnosed as such. The DIMCA Project*, for example, showed that the rise in the number of people presenting to GPs with respiratory complaints exceeded the rise in the actual prevalence of the complaints, as repeatedly determined in (cross-sectional) epidemiological studies of the same population.[83] One possible explanation for this is that the study made GPs and patients in the Nijmegen area (where the study took place) more alert to the possibility of an asthma diagnosis. A questionnaire-based epidemiological study carried out in the Netherlands and Germany found that GPs in the Netherlands were more likely to diagnose and treat a given set of symptoms as asthma than their German counterparts.[84] Another factor that may have contributed to the apparent rise in the prevalence of asthma in the Netherlands is the disuse of the term 'CARA**' since the early 1990s.[79] Certainly, the rise in asthma-related hospitalisations among children was accompanied by a clear decline in COPD-related admissions***.

The higher incidence of allergic rhinitis observed in the context of the Dutch National Study of General Practice may also be attributable partly to changes in data registration practices. The classification of allergic rhinitis**** has not changed since 1987, but in 1987 data were recorded manually, whereas the procedure was automated by 2001. Furthermore, in 1987 the practice was to monitor the incidence for three months, and then to extrapolate annual data. Given the

* DIMCA: Detection, Intervention and Monitoring of COPD and Asthma.
** CARA: chronic aspecific respiratory disease (asthma and COPD).
*** COPD: chronic obstructive pulmonary disease.
**** On the basis of ICPC code 97: hay fever/allergic rhinitis.

seasonal nature of hay fever, this practice may also have introduced an element of bias. It is also likely that the introduction of the NHG standards and publications* in the mid-nineties influenced data registration practices.

The changes in the reported incidence and prevalence of atopic eczema are more difficult to assess. It is difficult to diagnose atopic eczema in the context of questionnaire-based epidemiological studies, since there is no definite diagnostic criterion that one can apply.

The Committee concludes that the prevalence of asthma and allergy has been determined in various ways in the context of the various epidemiological studies and general practice data registration systems, and that the methodological differences account for the inter-source discrepancies in the prevalence figures. Prevalence changes over time detected within a given study design or health registration system are less likely to be attributable to artefacts. Nevertheless, changes in the classification methods and diagnostic criteria in the mid-1980s did probably give rise to artefacts. Furthermore, developments in the prevalence of asthma and allergy may be the result of changes over time in the public's awareness of these disorders and inclination to seek medical assistance with them.

Changes in public awareness and behaviour

It is often difficult to distinguish between a true rise in the prevalence of a disease and an apparent rise brought about by greater awareness on the part of patients or GPs. The Committee therefore considers it important to monitor changes over time not only by reference to general practice data registration systems, but also by means of epidemiological surveys.

Changes in sensitivity to inhalation allergens

One way of establishing the extent to which there have been true changes in the prevalence of asthma and allergy is to monitor change in objective clinical markers, such as bronchial hyperresponsiveness or sensitisation. To this end, such markers need to be measured repeatedly in representative groups of subjects using standardised methods. Too little monitoring work of this kind has so far been done in the Netherlands to support firm conclusions. Nevertheless, studies conducted in other countries provide more evidence *for* a slight increase in the prevalence of bronchial hyperresponsiveness and sensitisation than *against* such a rise.[85-87] However, the rise appears to be much smaller than the apparent increase in levels of asthma and allergy.

* NHG: Netherlands Association of General Practitioners.

Because the apparent increase in asthma and allergy symptoms in the later decades of the twentieth century was observed in the context of various studies of a similar design, the Committee is disinclined to attribute the rise entirely to diagnostic artefacts. Furthermore, given that changes in the genetic makeup of the population are inherently gradual, changes in the western lifestyle and everyday environment seem likely to be the principal drivers of the increase.

3.4.2 Stabilisation since the late 1990s

Since 1999, the prevalence of GP-diagnosed asthma appears to have stopped increasing among children in the Netherlands.[2] The latest data from the Nijmegen CMR* programme point to a similar levelling off of the diseases prevalence among adults aged twenty-five and older. Studies conducted in other countries are now starting to suggest that, following a sharp rise in the later decades of the last century, a plateau may have been reached in the prevalence of asthma and allergy.[72,88-90] However, it is not yet clear to what extent these findings reflect a true change in the frequency with which the illness occurs, as opposed to a more cautious approach to its diagnosis. It is also possible that the apparent stabilisation may be attributable to more widespread use of inhalant corticosteroids, leading to fewer people presenting to their GPs with asthmatic complaints and consequently to fewer recorded asthma cases.[2,75,88] Such medications cannot, however, be responsible for developments in the prevalence of (other) allergic disorders that they are not used to treat.[91] Another possibility is that a sort of 'saturation point' – i.e. a situation where most people with a predisposition towards asthma and allergy are now subject to the relevant lifestyle and environmental determinants and do therefore develop the disorders – has been reached. If that is indeed the case, it is likely that the prevalence of these disorders has reached a plateau. It is not possible to predict future developments in the prevalence of asthma and allergy on the basis of the data presently available.

3.5 Conclusions regarding changes in prevalence

Conclusions drawn from epidemiological surveys

Over the last few decades, a number of large epidemiological studies have been undertaken in the Netherlands. These studies have provided largely reliable data on the prevalence of respiratory complaints in preschool children, children of school age and adults. Fewer sound data are available concerning changes in the

* CMR: Continuous Morbidity Registration.

incidence of respiratory complaints and in the prevalence of lung function impairment, bronchial hyperresponsiveness, allergic sensitisation, allergic rhinitis and atopic eczema. This is partly because few studies into the prevalence of asthma and allergy have been repeated after a time interval. The results of one questionnaire-based study that was repeated in the province of Limburg suggest that since the late 1990s there has been no further increase in the prevalence of asthma symptoms in the study population, which consists of children. None of the other epidemiological studies support any firm conclusion regarding an increase or decrease in asthma and allergy in the Netherlands.

Conclusions drawn from general practice registration data

Figures from general practice data registration systems indicate that GPs have diagnosed asthma or allergy in 2 to 3 per cent of the Dutch population at large. Although there is too much scope for over- or under-diagnosis to allow firm conclusions to be drawn regarding the actual prevalence of asthma and allergy, it is possible to observe developments in the prevalence of these disorders over time. Thus, the Committee concludes that there was a rise in the incidence of GP-reported asthma and (seasonal) allergic rhinitis during the 1990s, but that since then there has apparently been no further increase and there may have actually been a decrease. It is not, however, clear to what extent the downturn reflects a more cautious approach to the diagnosis of these disorders, as opposed to any true change in their prevalence. The changes in the prevalence of atopic eczema over time are even harder to explain.

General conclusion

The data from repeated epidemiological surveys and those from general practice data registration systems are complementary in terms of what they tell us about changes over time in the prevalence of asthma and allergy. On the basis of all the available data, the Committee concludes that in the later decades of the twentieth century, asthma and respiratory allergy became more common in the Netherlands, but that the prevalence of these disorders has since ceased to increase and may even have decreased. The Committee believes that the initial increase in the apparent prevalence is attributable principally to a true rise in incidence, but to some degree also reflects developments in diagnostic practice. Much the same is likely to be the case where the recent apparent stabilisation is concerned. It is furthermore improbable that changes in diagnostic practice took place simultaneously in the various countries that recorded similar developments in prevalence. With a view to supporting firmer conclusions regarding future

trends, the Committee would like to see a number of successive studies performed using the same diagnostic criteria, so that the findings can be compared.

Chapter 4

The monitoring of asthma and allergy

The State Secretary's second request to the Health Council was as follows:

Can the Health Council specify the nature and size of any population groups that are at particular risk of developing asthma or respiratory allergy, and indicate how suitable the present monitoring programmes are for tracking the prevalence of these disorders in the high-risk groups geographically and over time?

The Committee has divided the State Secretary's request into the following component questions:

- What is the nature and size of any population groups that are at particular risk of developing asthma or allergy?
- Which indicators can practicably be used to monitor the occurrence of asthma and allergy?
- What programmes are presently in place for monitoring asthma and allergy?
- How adequate are these monitoring programmes, particularly in relation to the identified high-risk groups?

Each of the component questions is addressed in turn in the following paragraphs.

4.1 High-risk groups

In the context of this report, a high-risk group is a group of people who are more likely to develop asthma or allergy than the average person.

Heightened risk may derive from intrinsic risk factors (predisposition) and/or from exogenic risk factors (exposure to environmental factors). In this section, however, the Committee confined its attentions to high-risk groups whose members are congenitally predisposed to develop asthma or allergy.

Intrinsic risk factors

The key determinant of a person's reaction to exposure to the environmental factors associated with asthma and allergy is whether he or she has an atopic constitution (a hereditary predisposition to IgE-mediated allergic disorders).[92] The main high-risk group in this context is formed by children whose parents suffer from allergic disorders, such as asthma. Such children are three times as likely to develop such a disorder as their peers.[93] A German study found that 40 per cent of pre-school children with two asthmatic parents go on to develop asthma themselves; by contrast, only 10 per cent of pre-school children neither of whose parents suffer from asthma or allergy go on to develop such a disorder.[94] Nevertheless, the absolute number of child asthmatics whose parents do not have asthma or allergy exceeds the number of child asthmatics with one or two asthmatic parents.

Premature or low-birth-weight babies form a high-risk group for the development of non-allergic asthma in the first years of life.[95]

More generally, infants and toddlers constitute a high-risk group for asthma and allergy. The respiratory pattern and the anatomy and physiology of the respiratory tract of a neonate increase early sensitivity to environmental influences.[96,97]

Gender also has a bearing on a child's susceptibility to asthma symptoms. Boys – especially those whose fathers have asthma or hay fever – are apparently more likely to develop a wheeze than girls. This may, however, simply indicate that the disorder is under-diagnosed and under-treated in girls.[98] In adulthood, however, females – especially those whose mothers have/had asthma or hay fever – are more apt to wheeze than males.[99]

Finally, birth month has been identified as a predictor of sensitisation risk. Children born in the three months prior to the exposure peak for specific seasonal allergens, such as pollen and mites, are more likely to become sensitised than those born at other times of the year.[100-102] The evidence for a birth-month effect

supports the hypothesis that there is a period in the first phase of life, when a baby is particularly susceptible to allergens if exposed.

Other risk factors that are difficult to influence

Socio-economic status is not an intrinsic risk factor in its own right, but a sometimes unclear mixture of – difficult-to-influence – exogenic risk factors, including smoking. In the USA and Europe, asthma is *more* common – but allergy *less* common – in lower socio-economic groups than in higher groups.[103-105] However, no socio-economic differences in the prevalence of asthma have been detected in the Netherlands.[31] Because it is unclear to what extent socio-economic status is also an indicator of certain intrinsic risk factors, the Committee does not regard people of low socio-economic status or those of high status as constituting a high-risk group for asthma or allergy.

Other intrinsic and exogenic risk factors may be more common in certain non-western population groups. In school children of Surinamese, North African and Turkish origin living in Amsterdam, the prevalences of asthmatic complaints – in particular wheezing and attacks of breathlessness – were found to be lower than in children of indigenous origin in the period 1992/1993.[106] However, in the PIAMA study*, which took place the late 1990s, ethnic-minority parents reported more respiratory complaints in their children's first two years of life than other parents.[107] In 2000, the BOLA project** found that 24 per cent of the children of Turkish immigrants living in Utrecht, and 31 per cent of Moroccan immigrants' children, were sensitised to inhalation allergens (as determined by skin prick testing), compared with only 19 per cent of children in the host population.[108] However, in view of the diversity of prevalence levels, the Committee does not feel it would be justified to treat the ethnic-minorities as a high-risk group for asthma or allergy.

The Committee concludes that the main high-risk group for the development of asthma and allergy is formed by children of asthmatic or allergic parents. There is also evidence that low-birth-weight children constitute a high-risk group (albeit a relatively small one) for the development of asthma.

* PIAMA: Prevention and Incidence of Asthma and Mite Allergy.
** BOLA: Primary school Research Air pollution and Allergy.

4.2 Suitable indicators

Monitoring may be defined as the periodic measurement, analysis and interpretation of specific indicators.[109] In this report, we are naturally concerned with the measurement of asthma and allergy indicators. Where possible, distinction is made between indicators of allergic sensitisation, physical complaints and clinical diagnosis.

The monitoring of asthma and allergy has two aims:
- the early detection of people at raised risk, for the purpose of secondary prevention
- the tracking of changes over time in the incidence and prevalence of asthma and allergy.

In the context of this report, it is the second aim that is of particular significance. Therefore, the indicators advocated by the Committee are chosen primarily with this aim in mind. An asthma or allergy indicator is potentially valuable for tracking changes over time if it can be easily and validly measured, or if it is already being recorded in the context of one of the existing registration schemes. The most suitable indicators are examined in turn below.

Indicators that can be measured in epidemiological surveys

There are two kinds of indicators that can be measured in the context of (repeated) questionnaire-based studies or physical examinations and are capable of revealing changes in the prevalence of other symptoms of asthma and allergy in the population[110]:
- 'subjective' indicators or symptoms reported by the subjects in the context of validated questionnaires: ISAAC* for children and ECRHS** for adults
- 'objective' indicators based on diagnostic tests:
  - skin prick tests
  - specific IgE against certain allergens (sensitisation)
  - bronchial hyperresponsiveness
  - exhaled nitrogen monoxide*** (from primary school age).

* ISAAC: International Study of Asthma and Allergy in Children.
** ECRHS: European Community Respiratory Health Study (international ELON study network).
*** a non-invasive, distinctive and readily reproducible test for asthma-related respiratory inflammation [111-114]

Indicators employed in existing monitoring programmes

Data on the following indicators are presently routinely collected:

- GP-diagnosed asthma
- use of asthma or allergy medication
- asthma-related hospitalisation and mortality.

4.3 Monitoring programmes

The asthma and allergy indicators listed above are included or could be included in the following monitoring programmes.

4.3.1 General practice data registration systems

The general practice data recorded in the Netherlands do not support firm conclusions regarding the actual prevalence of asthma and allergy, because there is too much scope for over and under-registration. However, the data do support conclusions regarding changes in prevalence over time.

4.3.2 Dutch National Studies of General Practice

In 1987 and 2001, NIVEL* organised a National Study of General Practice. However, for a monitoring programme to properly track changes in the prevalence of asthma and allergy in general practice, the monitoring interval would need to be reduced.[109]

4.3.3 Drug use registers

The most promising medium for monitoring the use of asthma and allergy medication is the data registration programme operated by the Foundation for Pharmaceutical Statistics (SFK).[109] Because of the large number of individuals registered, the data can also be analysed at a low aggregation level. About 90 per cent of the nation's pharmacies participate in the programme and the number is rising.[115] Furthermore, the SFK has the largest body of data on this topic in the Netherlands. The drawback of drug use as an indicator is that it does not necessarily directly reflect the prevalence of the associated disorder, concerning which no information is recorded by the SFK.[109] Where people aged over forty are concerned, it is difficult to distinguish between the use of medication (inhalers) for

* NIVEL: Netherlands Institute for Primary Health Care Research.

asthma and their use for COPD unless one has supporting anamnestic or lung function data. Such drug use therefore serves as a useful indicator only when monitoring asthma in children and young adults. Another problem is that the level of drug use depends partly on doctors' prescribing habits, which are not necessarily uniform.

4.3.4 Hospital records

The National Register of Hospital Admissions (LMR-Prismant), which includes data on hospital admissions and discharges, is useful only for monitoring changes over time in serious forms of asthma and allergy that require hospital treatment.[109]

4.3.5 Cause-of-death records

The cause-of-death records maintained by Statistics Netherlands (CBS) are quite suitable for monitoring changes over time in asthma-related mortality.[109] However, mortality is not a direct indicator of prevalence, since it depends partly on treatment practices. The (other) allergic disorders with which the Committee is concerned rarely if ever cause death; mortality statistics are not therefore helpful for monitoring such disorders.

4.3.6 Local and National Monitor of Public Health and Young People's Health

The Local and National Monitor of Public Health and Young People's Health is operated by the Netherlands Association of Municipal Health Services, RIVM, TNO Quality of Life and ActiZ (a body which represents care-sector enterprises).[109] This programme collects data from health questionnaires, which are conducted in most municipal or community health service regions every four years in line with the provisions of the Public Health (Preventive Measures) Act. The Committee believes that the programme has great potential in the context of asthma and allergy monitoring. On the advice of a number of Committee members, a standardised set of questions about asthma has recently been adopted for use in the context of the Monitor of Young People's Health. The questions are based on the International Study of Asthma and Allergy in Children (ISAAC).

4.4 Conclusions

The Committee regards the children of asthmatic or allergic parents as the main high-risk group for the development of asthma and allergy. Premature and low-birth-weight infants are also considered to be a high-risk group.

None of the existing monitoring programmes is in its own right capable of providing sufficient information about changes in the prevalence of asthma and allergy in the Dutch population.

If the municipal health services incorporate the recently developed asthma module into the questionnaire used in the context of the four-yearly Monitor of Young People's Health surveys, this should provide insight into future changes over time in the prevalence of asthma in children and may create opportunities for secondary prevention, i.e. early diagnosis and treatment. Because most children with asthma and allergy are the offspring of non-asthma and non-allergic parents, the monitoring of asthma and allergy in all children is likely to be more helpful than the separate monitoring of specific high-risk groups.

Chapter 5

Role of predisposition and environment

The third request posed by the State Secretary was as follows:

Can the Health Council indicate what is known about the contribution of and interactions between the various genetic and environmental factors that influence the development and increase of asthma and respiratory allergy? Where are the main gaps in our understanding of these matters?

Few matters have been the subject of as much speculation in recent years as the role of environmental factors in the development of asthma and allergy. In answering the State Secretary's request, the Committee has drawn particularly on what it regards as the most important reviews of the literature and other key publications, treating the findings of prospective studies as carrying the most weight. It is a feature of allergy and asthma that exposure to environmental factors is apt to change in response to the disorder itself, as sufferers seek to avoid the circumstances that trigger problems. This can distort the picture provided by cross-sectional or case-control studies, in which exposure data are collected retrospectively.

The aetiology of asthma and allergy is complex: the development of these disorders is a product of both hereditary predisposition and environmental factors. In subsection 5.1, the Committee summarises the roles played by various genes in the development of asthma and allergy. Subsection 5.2 outlines the role of the immune system in the development of allergic disorders. A discussion of the possible influence of various environmental factors that have been associated

with asthma and allergy in recent years follows in subsection 5.3. The Committee's conclusions on this topic are presented in subsection 5.4.

5.1 The role of genes

It has long been recognised that the development of asthma and allergy has a hereditary component: the children of asthmatic or allergic parents are more likely to acquire an allergy or asthma than other children. However, predisposition is not attributable to a single gene, but to a whole series.[116] Several 'candidate regions' of the human genome are involved in the development of asthma and allergy. A candidate region of the genome is more commonly inherited by people with asthmatic phenotypes than by others. In other words: such sections are liable to contain genes that contribute to the development of asthma and allergy.

In recent years, various research teams have performed so-called linkage analyses and genome wide screens with asthmatic or atopic phenotypes. Linkage analyses are excellent for studying families to ascertain whether certain chromosomal regions are inherited with asthma and, if so, which ones. It has been established, for example, that the relatives of asthmatics are more likely to inherit one or more genes for bronchial hyperresponsiveness located on chromosome.[117] In addition, various chromosome regions that may contribute to atopy have been identified on a genome wide screen.[118] Such a candidate region may contain ten to twenty million base pairs, depending on the number of 'markers' used for the genome wide screen. This equates to several hundred genes.

Following the linkage analysis and genome wide screen comes the time-consuming task of identifying the genes responsible for the linkage effect. This can be done by positional cloning: placing markers on increasingly small elements of the candidate region, until one has pinpointed one or more genes that give rise to the linkage effect. Alternatively, one can use the 'candidate gene' method. A candidate gene is a gene with a biologically plausible function in the development of asthma or allergy. By 2006, this method had been used to identify seven further genes (in addition to those previously known) believed to play a part in the development of asthma and allergy.[116] A new development in this field has been the switch from studying a single gene, to studying changes in a combination of genes, such as those involved in cell activation. A definitive conclusion concerning the genes that together determine whether and when a person develops asthma or allergy will, however, require a number of large-scale studies.

Expression of the protective or undesirable properties of certain genes depends on the level of exposure to relevant environmental factors. One example of interaction between genetic and environmental factors is the way that the

chromosomal regions responsible for asthma respond to exposure to tobacco smoke.

Example: passive smoking

Because smoking during pregnancy is known to promote asthma and bronchial hyperresponsiveness in children, the interaction between antenatal and neonatal exposure to tobacco smoke and the development of bronchial hyperresponsiveness has been investigated.[119] It was found that some of the chromosomal regions associated with asthma and bronchial hyperresponsiveness contain genes that find expression particularly when the subject is also exposed to cigarette smoke.[120] Not all the chromosomal regions involved in the development of allergic disorders participate in genetic-environmental interaction of this kind, however.[121]

The observation that a given genetic predisposition could lead to various forms of asthma and allergy, depending on the environmental factors present has led to the supposition that the innate (aspecific) immune system plays a critical role in genetic-environmental interaction.[122,123] Although the scientific community has learnt a great deal in the last ten years about genetic predisposition to asthma and allergy and the variations therein, the practical significance of this knowledge for the expression and prevention of such allergic disorders remains unclear.[124,125]

5.2 Role of the immune system

In section 2, an allergy was defined as an immune-mediated hypersensitivity reaction, giving rise to raised levels of specific antibodies, usually of the type E (IgE). Antibodies are produced by B-lymphocytes, but the production process depends to a significant extent on the activity of T-lymphocytes, which are themselves incapable of producing antibodies.[126] The activity of T-lymphocytes is in turn dependent on so-called dendritic cells*. Micro-organisms and microbiological agents have a particularly great influence on dendritic cells and therefore indirectly** on the formation of antibodies.

The immune system can be divided into an aspecific 'innate' system and a specific 'acquired' system.[127,128] Both systems contribute to immune regulation. In the immune system, so-called T helper cells play a regulating role. Ordinarily, there is an immunologic balance between various types of T helper cell, in particular between Th1 cells and Th2 cells. At birth, the innate Th2 cells – the source

* Dendritic cells: cells that recognise xenobiotic components (antigens) and present them to the B and T lymphocytes of the acquired immune system.

** By means of an immunologically innate, aspecific stimulation of, amongst other things, the Toll-like receptors of the dendritic cells and the release of interleukins and other messenger proteins.

of ‘maternal immunity’ – predominate; then, as the infant is exposed to infectious illnesses and other environmental factors, the Th1 cells – which provide acquired immunity – become increasingly prominent.

Under certain circumstances, allergen-induced IgE-mediated reactions result in the large-scale release of interleukins and cytokines, which have a suppressant effect on both Th1 and Th2 cells, thus preventing undesirable allergic reactions. The release of these suppressant immuno-modulating or anti-inflammatory agents in sufficiently high concentrations, as previously observed in response to worm infections, is controlled by T regulator cells.[129,130] It has therefore been suggested that reduced exposure to ‘old friends’, such as worm infections, mycobacteria (including tuberculosis) and lactobacilli, means that the function of the T regulator cells is compromised, and that this is the reason for the growth of allergic reactions in western countries.[131]

Microbiological factors often stimulate the production of antibodies, but they can also have the opposite effect.[126] The intestinal flora, for example, has an important stimulatory effect. It has been observed that if the intestinal flora is absent during neonatal development of the immune system, laboratory animals are liable to suffer serious immune deficiencies. Furthermore, the presence of bacterial factors in a vaccine is known to strongly promote the formation of antibodies to the vaccine; this is known as an ‘adjuvant effect'. Most adjuvant effects are short-lived and localised, i.e. apparent only in the part of the body where exposure occurs. However, micro-organisms and microbiological agents also have systemic effects, particularly by means of a cytokine response.[132] The associated fever reaction can itself influence the immune response as well. The suppressant role of bacterial products is again most evident in the intestinal tract, where the flora makes an important contribution to the development of immunologic tolerance.[126] Without intestinal immunologic tolerance, serious local inflammation responses are liable to occur.

The effect of a microbiological stimulus in a human depends on various factors, such as the nature of the stimulus, its location in the body and the phase of life. Microbiological effects on the immune system have been studied mainly using bacteria and bacterial products, such as endotoxins. The effects of viruses, yeasts and fungi are less clear. Most of the information regarding the effects of parasites relates to multicellular tropical organisms such as Bilharzia and Filaria, which do not suppress the formation of IgE antibodies, but the effects of such antibodies.[131]

Contact with micro-organisms appears to be an important controlling factor in regulation of the immune system. This forms the basis of what has become known as the ‘hygiene hypothesis’, which seeks to explain the possible associa-

tion between exposure to bacteria, viruses and parasites and the development of allergic disorders. The hygiene hypothesis was introduced by Strachan, who reported that the chances of developing hay fever were inversely related to the number of older siblings a person had.[133] He postulated that this observation was attributable to higher levels of infectious illness in large families. The Committee regards 'hygiene' as insufficiently specific and considers it better to focus on specific micro-organisms and microbiological substances, such as bacterial endotoxins. The role of microbiological factors in asthma and allergy is considered more closely in subsection 5.3.1.

5.3 The role of environmental factors

It is believed that asthma and allergy are related to certain aspects of western lifestyle. Some observers have suggested that the increasing prevalence of asthma and (other) allergic disorders in the later decades of the twentieth century was attributable to greater hygiene, increased immunisation or vaccination levels or reduced infection pressure resulting from a smaller average number of children per family.[134] Others have argued that the increase is more likely to have resulted from dietary changes, physical inactivity or greater exposure to environmental factors, which may be divided into allergic and non-allergic stimuli.[135,136]

Since the 1990s, several prospective birth cohort studies have been started in the Netherlands and elsewhere in Europe, with the aim of identifying influenceable risk factors* in the development of asthma and allergy among children.[137,138] Prospective studies enable the relationship between exposure and development of the disorder to be characterised. This subsection is devoted largely to the findings of the various cohort studies. The results of relevant clinical trials are discussed in section 6. Below, the Committee summarises what is presently known about the influence of environmental factors, addressing each of the following in turn:

- microbiological factors
- allergens
- breastfeeding
- diet
- overweight
- prematurity and low birth weight
- outdoor air pollution
- indoor air pollution.

* The risk factors that are not subject to influence are dealt with in subsection 4.1, regarding at-risk groups.

5.3.1 *Microbiological factors*

Various microbiological environmental factors play a role in the development of asthma and allergy. These may be divided into two broad groups: micro-organisms (intestinal flora, gastrointestinal infections, respiratory infections and indirect indicators of exposure to micro-organisms, known as proxy variables) and non-infectious microbiological agents: bacterial endotoxins and fungal agents.

Micro-organisms

Intestinal flora. A study of a cohort of forty-four infants in Sweden and Estonia revealed that the children who in the first two years of life became sensitised or developed atopic eczema differed from their unaffected contemporaries in terms of their intestinal flora.[139] The intestines of infants who developed allergies were more extensively colonised by Clostridia, for example, but less by Bifido bacteria. In a Finnish cohort of seventy-six children, similar anomalies were discovered several weeks after birth in the intestinal flora of those who later developed allergic symptoms.[140] In a review it was suggested that there are various indications that the intestinal flora and the immune system of the intestinal wall can play an important role in the prevention of allergic disorders.[141]

Gastrointestinal infections. A number of cross-sectional studies of adult populations have suggested that certain gastrointestinal infections are associated with a lower prevalence of asthma, allergic rhinitis and eczema.[142-145] However, the effect on sensitisation can differ, depending on the micro-organisms involved. A Danish study found evidence, for example, that exposure to Campylobacter or Yersinia increased the prevalence of sensitisation to respiratory allergens, while exposure to hepatitis A, Helicobacter pylori and Toxoplasma gondii, was associated with a lower prevalence of sensitisation to such allergens.[146]

Respiratory infections. From the evidence presented in several reviews, it seems probable that Respiratory Syncytial Virus (RSV) infection in infancy is associated with a raised subsequent risk of developing asthma.[147-150] It is unclear, however, to what extent this also influences the development of allergy. Since the appearance of these reviews, the findings of a number of prospective studies have been published, confirming the reported association. A British prospective cohort study (ALSPAC*) has found that hospitalisation in the first year of life because of confirmed RSV-related bronchiolitis, was associated with a greater likelihood of asthma by the age of seven, but not with a greater likelihood of sen-

* ALSPAC: Avon Longitudinal Study of Parents and Children.

sitisation, as determined by skin prick testing.[151] In a Finnish study involving the follow-up after a twelve-year interval of children who had been hospitalised because of serious respiratory complaints in the first two years of life, it was found that RSV-related hospitalisation was strongly associated with subsequent asthma.[152] A prospective study in Sweden revealed that infant hospitalisation because of RSV bronchiolitis was associated not only with asthma symptoms at the age of twelve, but also with sensitisation to common inhalation allergens.[153] Little is known about the influence of other respiratory infections on the development of asthma or allergy.

Proxy variables of exposure to micro-organisms

The various known associations between asthma or allergy and direct indicators of exposure to micro-organisms have been summarised above. However, associations have also been reported with a number of indirect indicators of exposure to micro-organisms, known as proxy variables.

Vaccinations. The first proxy variables are vaccinations. If infection at an early age inhibits the development of allergy, it is plausible that large-scale vaccination could increase the risk of people developing allergic asthma and other allergic disorders. Such an effect could result either from the direct influence of vaccination on the immune system, or from the reduced infection pressure. However, vaccination with living attenuated vaccines might be expected to have the opposite effect.

A Dutch questionnaire-based study carried out in 2003-2004 with a homogeneous group of eight to twelve-year-old children (n = 1,875) at strict reformed Christian primary schools found no association, even after correction for confounding factors, between vaccination against diphtheria, whooping cough, tetanus, polio and *Haemophilus influenzae* type b and the development of asthma, hay fever, eczema or food allergy.[154,155] An earlier study by the same investigators, involving 1,724 six-year-old children (born in 1988-1990), found that children who had been vaccinated against whooping cough were less likely to develop allergic disorders than children who – for faith reasons – had not been vaccinated.[156]

The results of several retrospective cohort studies performed in other countries, suggest that early vaccination with living attenuated vaccines, such as the tuberculosis vaccine BCG, tends to reduce the risk of subsequently developing asthma and allergy symptoms, particularly in children with an allergic predisposition.[157-159] However, various other studies have found no association between BCG vaccination and a lower prevalence of allergic disorders.[160]

Although, generally speaking, prospective studies carry more evidential weight, bias can occur in the results of prospective studies involving specific study populations. In orthodox Christian communities, for example, the prevalence of asthma and allergy could be affected not only by aversion to vaccination, but also by factors such as family size or inclination to consult a doctor. The investigators performing a prospective birth cohort study in the UK reported that doctor-diagnosed asthma and eczema were more common among vaccinated children than their unvaccinated peers.[161] However, this association was apparent only among the children who were taken to the doctor least frequently in infancy. The investigators attributed the association to the under-diagnosis of allergic disorders in unvaccinated children. In another prospective birth cohort study in the UK, no association was detected between vaccination and the development of asthma or eczema.[162] Furthermore, two Dutch reviews written in 2004 concluded that there was no evidence that vaccination had an undesirable effect on the development of allergic disorders.[163,164]

Antibiotics. The possibility that antibiotics could affect the development of asthma and allergy is still the subject of debate. Some cross-sectional and retrospective studies have detected an association between the use of antibiotics and allergic disorders.[165,166] An association has also been found between antenatal exposure to antibiotics and the development of allergy.[167] This finding is consistent with the conclusions of earlier studies into the relationship between infections during pregnancy and the child's subsequent development of allergic disorders.[168,169] On the other hand, three prospective studies suggest that the association actually entails 'reversed causality': the same infections that necessitate the prescription of antibiotics can also induce asthma.[170-172] Two reviews published in 2004 and 2006 concluded that the antibiotic-related risks observed in prospective studies are in fact lower than those observed in cross-sectional studies and not statistically demonstrable.[173,174]

Antipyretics. A review published in 2005 concluded that there was convincing evidence of a dose-response relationship between antenatal exposure to paracetamol and the development of asthma, rhinitis and eczema in childhood.[175] Even after correction for confounding factors, a statistically significant association remained. Furthermore, the association was confirmed by studies performed not only in Europe and the USA, but also in Ethiopia. Because users of other antipyretics, such as acetylsalicylic acid, were admitted to the control group, reversed causality cannot explain the observations, as was the case with the use of antibiotics. Data from the prospective ALSPAC cohort study* were used to

* ALSPAC: Avon Longitudinal Study of Parents and Children.

calculate that in this population frequent (almost daily) use of paracetamol in the second half the pregnancy term could account for several percentage points of the asthma prevalence in young children.[176] This may be because paracetamol works as an oxidant.

Other proxy variables. Numerous studies have focused on other proxy variables of exposure to infections, such as position in the family (birth order), family size or nursery attendance.[160] Because such indicators are very indirect, and merely assumed to have an unmeasured influence on infection pressure, the Committee prefers not to draw any conclusions from this type of studies concerning the role of microbiological factors in the development of allergic disorders.

Non-infectious microbiological agents

The phrase 'non-infectious microbiological agents' is used by the Committee to denote material of bacterial or fungal origin, which can cause inflammation and/or influence the immune system's response to allergens. It is believed that exposure to non-infectious microbiological agents inhibits the development of asthma and allergy.

Bacterial endotoxins. Bacterial endotoxins are material from the cell walls of gram-negative bacteria. A cross-sectional study conducted in Germany, Austria and Switzerland demonstrated an inverse dose-response relationship between the concentration of endotoxins in the mattress dust of children growing up on farms and the likelihood of sensitisation, hay fever and allergic asthma.[177,178] The PARSIFAL study – another cross-sectional study, involving centres in Germany, Austria, Switzerland, the Netherlands and Sweden – found that farm children were about half as likely to become sensitised or suffer allergic rhinitis as children who lived in a rural area, but not on a farm.[179] The domestic dust on farms was shown to contain three times the concentrations of bacterial and fungal materials found in dust from other homes. In this study, no distinction could be made between exposure to endotoxins and exposure to fungal agents, such as glucans and extracellular polysaccharides.[180]

However, other cross-sectional studies have indicated that endotoxins can have an adverse effect on asthma symptoms. A Belgian study carried out in the late eighties produced evidence that the presence of endotoxins in domestic dust was associated with poorer health among asthmatics.[181,182] Furthermore, the PARSIFAL study found that, among the children of anthroposophical parents, a higher concentration of endotoxins in domestic dust tended to be associated with the presence of allergic asthma.[183] The findings of a cross-sectional study in the USA showed an association between the concentration of endotoxins in domestic

dust and both the prevalence of asthma and the use of asthma medication.[184,185] In addition, occupational exposure to high airborne endotoxin concentrations, as experienced by pig farmers, can apparently lead to occupational asthma, serious respiratory inflammation, bronchial hyperresponsiveness and loss of lung function.[186-188]

The results of prospective studies of the role of endotoxins in domestic dust are not always consistent either. A study performed in Boston yielded evidence that exposure to high endotoxin concentrations was associated with a lower rate of eczema in the first year, but only among children with allergic or asthmatic parents.[189] By contrast, older siblings who had been exposed to high endotoxin concentrations since birth were actually more likely to develop asthmatic complaints later in life and liable to exhibit impaired interleukin production.[190] Certain interleukins are believed to inhibit the development of allergic disorders.[191] The Dutch PIAMA cohort study* found that asthma was less common in children exposed to higher dust concentrations of endotoxins and fungal agents in the first year of life.[192] These findings are at odds, however, with the results of a German-Scandinavian study.[193,194]

An explanation for the inconsistent findings of studies into the effects of exposure to endotoxins may lie in the genetic-environmental interaction.[195,196] Such interaction may be variable in its form as a result of the polymorphism** of the CD14 gene, which influences the immune response to endotoxins. Children with the TT genotype have lower levels of circulating soluble CD14 and lower levels of IgE in their serum.[197]

However, not all the studies that have looked for an association between the T allele*** and the risk of developing allergy have found an inverse relationship.[198] The T allele is, for example, also associated with heightened risk of allergy in children growing up on farms.[199] Variations in the interaction between genetic predisposition and exposure to environmental endotoxins may explain why the T allele appears to be a risk factor in one population and a protective factor in another.[196] A case-control study of asthmatics and their families showed that the TT genotype tended to protect against the development of asthma among people who grew up in a low-endotoxin environment, but was associated with elevated risk among those exposed to high levels of endotoxins.[200]

Various reviews have concluded that early exposure to endotoxins inhibits the development of sensitisation, allergy and asthma, but that endotoxins are

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* PIAMA: Prevention and Incidence of Asthma and Mite Allergy.
** Polymorphism: the existence of various genetic variants.
*** Allele: a polymorphic variant of a gene.

associated with an increased risk of aggravating existing respiratory complaints.[201-206] It is unclear, however, to what extent endotoxins themselves play a causal role. The Committee accordingly recommends further research into the critical exposure period and into the underlying immunologic mechanisms.

Fungal agents. Fungal agents also appear to be capable of causing inflammation or influencing the response of the immune system to allergens. However, testing for and identifying viable (colony-forming) fungal material is a time-consuming and therefore costly business, and the reproducibility of the process is very poor. Research teams have consequently focused on readily detectable fungal agents, such as ergosterol, extracellular polysaccharides (EPS) and $\beta \rightarrow 3$ glucans. A Dutch case-control study found that children with chronic respiratory complaints were more likely to live in a home with a relatively high concentration of EPS in the dust on the living room floor, but more likely to sleep on a mattress with a relatively low dust EPS concentration.[207] The concentrations of fungal agents and house dust mites proved to be higher in homes with fitted carpets and in homes that were regarded as damp. Another Dutch study indicated that high $\beta \rightarrow 3$ glucan concentrations in the living room carpet were associated with greater variability in the peak flow in children with asthma.[208] A summary of what is presently known about $\beta \rightarrow 3$ glucans has recently been published.[209] The author concludes that the studies conducted to date does suggest some association between domestic exposure to $\beta \rightarrow 3$ glucans and respiratory symptoms, but that a proper understanding of the relationship is impossible without large-scale epidemiological studies using properly validated exposure indicators.

The Committee concludes that no consistent association has been demonstrated between infection in infancy and the development of sensitisation or allergy. However, the Committee does not exclude the possibility that some non-infectious microbiological agents can protect against the development of allergic disorders.

5.3.2 *Allergens*

Agents that are capable of causing allergy are referred to as allergens. However, allergens do not trigger allergic reactions in everyone exposed to them. This report is concerned particularly with inhalation allergens and devotes only marginal attention to food allergens, since the Health Council has already reported on the latter.[13] Another Health Council report is shortly to be published, dealing with the standardisation of allergenic substances, which will deal at more length with certain matters surrounding occupational exposure to allergens. Exposure to

inhalation allergens increases the risk of sensitisation and the development of allergic respiratory complaints. Both high-molecular-weight biological agents (proteins) and low-molecular-weight chemical agents can act as allergens.[14]

Inhalation allergens of chemical origin

Chemical allergens, such as certain heavy metals, diisocyanates, acid anhydrides and reactive colouring agents can combine with the body's own proteins to form hapten-carrier complexes and thus induce allergy. It is not yet clear what characteristics a chemical must possess in order to be capable of acting as an inhalation allergen.[210] Nor is it clear to what extent exposure to volatile organic compounds* emitted by sources in the everyday environment, such as petrol, tobacco smoke or other combustion products, paint, dry cleaning, soft furnishings or building materials contributes to the development of respiratory hypersensitivity.[211] Animal studies have produced evidence that the intranasal administration of known low-molecular-weight inhalation allergens can cause symptoms of allergic rhinitis and other effects, such as a rise in total IgE.[212]

Inhalation allergens of biological origin

Various inhalation allergens from animals or plants play an important role in the early development of asthma and allergy.[213] Sensitisation to the house dust mite or domestic pets is a major asthma risk factor.[214,215] Some studies have produced evidence that early exposure to allergens from, for example, house dust mites and cats increases the risk of sensitisation to the allergens in question.[216-219]. The Dutch PIAMA study found that, in the children of allergic mothers, relatively high levels of exposure to mite, dog and cat allergens were associated with an increased risk of wheezing by the age of four.[218] Various studies have examined the effects of specific inhalation allergens.

House dust mites. A Dutch cross-sectional study revealed that the concentration of house dust mite allergens was between six and fourteen times higher in the dust on textile floor coverings than in the dust on smooth floor coverings.[220] Furthermore, there was a statistically significant association between the mite concentrations in the floor coverings and the age of the home and its floor coverings, the number of household members and the absence of floor insulation. The concentrations of house dust mite allergens were significantly lower in homes with continuous mechanical ventilation.

* Volatile organic compounds include methane, benzene, toluene, ethylene, xylenes, trichloroethylene and tetrachloroethylene.

Prospective studies into the effects of exposure to house dust mite allergens have produced contradictory results. A prospective Taiwanese study found that early exposure to house dust mite allergens was associated with an increased risk of atopic eczema by the age of three, but not with an increased risk of asthma.[221] A European multi-centre birth cohort study was unable to detect any relationship between early exposure to house dust mite allergens and wheezing at the age of four.[222] Investigators in the USA following a small birth cohort of children who at birth exhibited raised umbilical cord IgE levels found no association between early exposure to mite allergens and asthma or bronchial hyperresponsiveness at the age of seven.[223] The Committee concludes that early exposure to house dust mite allergens may increase the risk of atopic eczema, but that there is no evidence to suggest that it increases the risk of asthmatic complaints in the early years of life.

Domestic pets. Studies into the role of domestic pet allergens has yielded similarly conflicting evidence. Several retrospective and cross-sectional studies have indicated that contact with domestic pets tends to protect against asthma and allergy symptoms.[224-231] On the other hand, two large-scale cross-sectional-studies in the USA found evidence of an adverse association between the presence of domestic pets or domestic pet allergens and the development of asthma symptoms.[232,233] Furthermore, the nature of the observed effects differs from one kind of animal to another. The European Community Respiratory Health Survey (a large study involving 18,530 subjects) discovered that growing up in a home where there were cats increased the risk of developing (allergic) asthma among sensitised people, particularly if there were few cats in the wider everyday environment.[234] Among non-sensitised people, living with dogs brought a greater risk of (non-allergic) asthma, but reduced the likelihood of developing hay fever. The latter observation supports the theory that a high background exposure can induce tolerance to allergic disorders.[235]

If a family member has an allergy, it is common that actions have been taken within the household to reduce his/her exposure to the relevant allergens. This tends to diminish the informative value of retrospective or cross-sectional studies by giving rise to a reverse causality effect.[227,236-240] The Committee therefore believes that priority should be given to prospective studies. However, even in a prospective study, the possibility cannot be excluded that exposure to domestic pet allergens is lower in families with an allergic constitution.[241] A child at increased risk of allergy is more likely to spend time in an environment where the allergen concentrations are relatively low because, for example, parents with a family history of allergy are less likely to have a pet.[238,242]

A number of prospective studies have detected that contact with domestic pets or domestic pet allergens tends to protect against sensitisation, atopic eczema or wheezing.[243-246] In a cohort study in Boston, it was observed that the presence of a cat or dog in the home during the first four years of life inhibited the development of asthmatic complaints (wheezing), while a high concentration of bacterial endotoxins in domestic dust was associated with an increased risk of such complaints.[190] These findings suggest that contact with domestic pets and exposure to endotoxins have distinct, contrasting effects, despite the fact that pet ownership is associated with exposure not only to domestic pet allergens, but also to endotoxins. In Sweden, the BAMSE birth cohort study provided evidence that the presence of a dog in the home reduced the risk of sensitisation to inhalation allergens and asthma by the age of four.[247] The presence of a cat increased the likelihood of sensitisation to cat allergens, but did not reduce the likelihood of asthma. In another Swedish birth cohort study, dog ownership was found to proffer a degree of protection against the development of pollen allergy and wheezing in the first four years of life.[248] The findings of a Danish multi-centre birth cohort study indicated that children born into a family where there were domestic pets were less likely to develop atopic eczema in the first eighteen months of life.[249] A birth cohort study carried out in Wisconsin found evidence that dog ownership inhibited both sensitisation and the development of atopic eczema in the first year of life.[250] This effect was accompanied by a stronger immune response, as reflected in interleukin and cytokine secretion, which may work against the development of allergy. Data from a small-scale birth cohort study in the UK suggested that the likelihood of sensitisation and asthma increased following early exposure to cat allergens in relatively low concentrations, but fell as the exposure concentration rose, particularly in children with a family history of such disorders.[251]

Another prospective study found no such protective effect, however.[252-254] The European multi-centre birth cohort study produced evidence of a relationship between early exposure to cat allergen and wheezing at the age of four, albeit mainly in children whose mother were asthmatic.[222] In the German prospective Multi-centre Allergy Study (MAS), sensitisation to cat allergens was clearly associated with wheezing and bronchial hyperresponsiveness up to the age of seven.[219]

A review published in 2005 concluded that children who grew up with domestic pets exhibited an immune response that made them less likely to become allergic.[255] However, because not all studies were able to find any inverse association between contact with domestic pets and the development of asthma or allergy symptoms, and because few investigators made adequate

allowance for the fact that many households that include an allergic individual do not keep domestic pets, the Committee takes the view that the evidence is not strong enough to conclude that contact with domestic pets is or is not advisable in preventing allergic disorders.

Vermin. In the USA, sensitisation to allergens from vermin, such as of mice and cockroaches, has been identified as a risk factor for asthma symptoms.[256,257] A cross-sectional study involving the analysis of umbilical cord blood from 167 neonates in downtown New York revealed that, prior to birth, more than half of the infants had been sensitised to cockroaches and a third to mice.[258] A prospective study in Boston found that early exposure to cockroach allergens was associated with a higher incidence of wheezing in the first year of life.[257] A similar effect was seen where there were mice in the house. In US inner cities, nearly 70 per cent of children with moderate to serious asthma are sensitised to cockroaches.[259] Among such children, exposure to cockroach allergens led to a statistically significant rise in asthmatic complaints, and was responsible for more asthma-related morbidity than exposure to allergens from house dust mites or domestic pets.

Dutch investigators compared the IgE status for a number of allergens in forty-six parent-child pairs whose homes had recently been treated to remove cockroaches.[260] In 44 per cent of the forty-six homes, cockroach allergens were still detectable. Seven adults and one child were found to have raised levels of IgE against the German cockroach. In the same study, the IgE status was determined of children in three groups (n=76) whose homes had no history of infestation. Four per cent of the children without respiratory complaints, 16 per cent of the children with respiratory complaints and 48 per cent of the children with two or more raised IgE levels were found to have raised anti-cockroach IgE. Sixteen of the eighteen children with raised anti-cockroach IgE also had an elevated level of IgE against the house dust mite.

Fungi. Only a small number of studies have been conducted into the effect of fungal allergens on sensitisation and asthmatic complaints. In the Boston cohort, an association was detected between the concentration of a number of specific fungal spores in the air and the incidence of lower respiratory tract illnesses in the first year of life.[261] An Australian cohort study found that higher concentrations of fungal spores in the indoor atmosphere were associated with an increase in the frequency of asthma attacks and sensitisation.[262] In a Dutch study involving 137 ‘atopic’ children aged between five months and fourteen years, the prevalence of sensitisation to fungi, including Alternaria and Cladosporium, proved to be 14-18 per cent.[263] The distribution was age-dependent with the peak at 7.8 years. However, Finnish investigators found that the level of sensitisation to

Alternaria and Cladosporium in patients with allergic disorders was less than 3 per cent and involved mainly people who were sensitised to various allergens.[264]

Pollen. An association has been observed between high levels of neonatal exposure to birch pollen and both sensitisation to this allergen in pre-school children and higher rates of pollen-related and domestic pet-related asthma.[265] However, maternal pollen allergy proved to be a more reliable predictor of such disorders in the children than direct exposure.[266] As long ago as 1990 and 1992, Dutch investigators demonstrated that birth in the three months prior to the relevant allergen concentration peak was associated with an increased risk of sensitisation to each of three seasonal allergens (beach pollen, grass pollen and house dust mites).[100,267]

Recently inconclusive evidence has emerged that ambrosia pollen* levels have increased in the Netherlands.[268] Because these pollen are being spread mainly in September and October and possess several times the allergenicity of grass pollen, the further spread of this plant, promoted by recent warm autumns, could extend the hay fever season. In addition, climate change could bring about a more general increase in pollen levels and the prevalence of the associated allergic disorders.[269,270]

In summary, early exposure to inhalation allergens does not necessarily increase the risk of sensitisation. Furthermore, the dose-response relationship varies from one allergen to the other. The relationship between exposure to an allergen and the development of asthma is even less straightforward. The evidence for the protective effect ascribed by some investigators of high levels of exposure to animal allergens is not strong enough to persuade the Committee that early contact with animals is advisable to prevent asthma or allergy. What is clear is that, once sensitisation has occurred, it is a major risk factor for the development of asthma and that high levels of exposure to allergens are undesirable for sensitised individuals. However, the notion that elevated exposure increases the risk of sensitisation and thus the risk of asthma has proved simplistic.

Food allergens

Food allergens are considered in great detail in another report recently published by the Health Council.[13] The Committee has therefore confined itself to the question of the extent to which the early acquisition of a food allergy (typically to

* Ambrosia: a plant of the Composite family that originated in North America and is now spreading across Europe; globally, Ambrosia is one of the main causes of hay fever.

cow's milk or hen albumen) is associated with the subsequent development of respiratory allergy and asthma. The early development of allergy to cow's milk and hen's eggs, and the subsequent development of respiratory allergy and asthma is often referred to as the 'allergic march' or 'atopic march'.[271] The prospective Multi-centre Allergy Study (MAS) found that children who were sensitised to hen's eggs at the age of one year were more likely to become sensitised to inhalation allergens in the following two years.[272] The follow-up of a birth cohort of 2,600 children in Australia revealed that introduction to food allergens prior the age of four months increased the likelihood of asthma at the age of six years by 35 per cent.[273] A Finnish study of children diagnosed as having a food allergy in infancy concluded that the incidence of asthma, allergic rhinitis and eczema at the age of ten years was three to four times higher in the study group than in the control group.[274] More recently, the results have been published of a long-term follow-up of Finnish children, who had been diagnosed with a clinically confirmed cow's milk allergy by the age of seven months.[275] At the median age of 8.6 years, children with early-manifestation cow's milk allergy were much more likely to be sensitised to inhalation allergens and to suffer from asthma, hay fever and atopic eczema than their control-group peers. These findings were independent of the presence of asthma or allergy in the parents.

Breastfeeding

Exclusive breastfeeding (i.e. breastfeeding without additional feeding) for at least three to four months inhibits sensitisation and the development of atopic eczema or asthma in the early years of life. That is the conclusion of numerous meta-analyses and reviews of numerous large, well-designed birth cohort studies, among which the Dutch PIAMA study.[276-283] The beneficial effect of exclusive breastfeeding is usually even more pronounced in children with an atopic constitution. However, exclusive breastfeeding for six months or longer does not demonstrably increase the protective effect.[284]

The duration of the effects of breastfeeding remains unclear. A German birth cohort study (n=1,314) observed a statistically significant increase in the prevalence of atopic eczema in the first seven years of life. The increases equated to three per cent for every additional month of breastfeeding.[285] The findings of this study were corrected for parental allergies, which tend to influence the duration of breastfeeding. The results of a long-term prospective study in New Zealand support the observation that breastfed children exhibit an increase in allergic disorders later on.[286] Again, the results were adjusted for parental asthma or allergy. However, neither the duration nor the exclusiveness of the breastfeeding was adequately defined in this study.[287]

Although there is doubt concerning the duration of the effect, the Committee concludes that it is probable that exclusive breastfeeding for at least three to four months reduces the risk of developing asthma or allergic disorders.

5.3.3 *Diet*

Diet is one of the factors that can play a role in the development and aggravation of asthma.[288-293]

Antioxidants play an important role in protecting the respiratory epithelium against damage due to oxidative stress.[292] There is a fairly consistent body of evidence that fruit and vegetables protect against childhood asthma. In adults, the observed beneficial effects mainly involve improved lung function; there seems to be less benefit where other indicators of asthma are concerned. It is not clear whether the beneficial effects of fruit and vegetable consumption are attributable to the particular antioxidants they contain, such as vitamin C, or to the healthier lifestyle typically associated with high fruit and vegetable intakes.

It is biologically plausible that the consumption of fish oil fatty acids (n-3 fatty acids) have a beneficial effect on immune regulation and help to suppress inflammation processes.[294] However, the evidence available from epidemiological studies is not sufficiently strong to be certain.[293]

The information so far published concerning the possible harmful effects of eating margarine or other vegetable foodstuffs with high concentrations n-6 fatty acids or trans fatty acids remains contradictory.[293] The most consistent observation concerning fatty foodstuffs is that the consumption of full-fat milk and butter in childhood is associated with the less frequent occurrence of asthma symptoms than the consumption of half-fat alternatives.[295,296]

The consumption of salt (sodium chloride) promotes the contraction of smooth muscle tissues and can therefore aggravate bronchial hyperreactivity and complaints, particularly in asthmatics.[297] However, most of the reported cross-sectional and case-control studies found no association between such disorders and salt intake.[293] In clinical trials involving asthmatics, a slight adverse effect on bronchial hyperresponsiveness has nevertheless been observed (see 6.1.2).

The Committee concludes that there are indications that certain substances in fruit and vegetables may protect against the development of asthma and allergy. The influence of fats and salt is less clear. The Committee does not believe that there is sufficient evidence to justify recommending the use of dietary supplements with a view to preventing asthma or allergy.

5.3.4 *Overweight*

There is some evidence that overweight can contribute to the development of asthma.[298]

In a large-scale cross-sectional study in the USA (NHANES*), an association was observed between bodyweight and asthma in children aged four to seventeen, but no association was found between bodyweight and sensitisation.[299] In the Swedish part of the ISAAC study**, however, overweight was associated with sensitisation in ten to eleven-year-olds.[224]

A number of prospective studies has also produced evidence that overweight increases the likelihood of asthma.[300] The association has been observed in both children and adults, even after correcting for various confounding factors, such as diet and hormone use. The link is stronger in women than in men. Two prospective cohort studies of school children in the USA found that the risk of asthma was particularly elevated in overweight girls, who also exhibited raised bronchial hyperresponsiveness during early adolescence.[301,302] A birth cohort study in Australia demonstrated an association between a high bodyweight and asthma symptoms in six-year-olds.[303] Furthermore, a recent meta-analysis has shown that high birth weight and high bodyweight during childhood increase the likelihood of asthma.[304] In children, high bodyweight may raise the asthma risk by as much as 50 per cent.

The relationship between overweight and asthma is complex. The observed effects may be explained by enhancement of the immune response resulting from elevated production of inflammation mediators due to the amount of adipose tissue.[305,306] Other possibly significant factors include common genes, sex hormones, dietary factors during pregnancy and reduced lung function. However, a recent review cast doubt on the apparent association between overweight and asthma in children, suggesting that investigators may simply have observed the over-reporting or over-diagnosis of asthmatic complaints in overweight children.[307]

5.3.5 *Prematurity and low birth weight*

Studies of various kinds have produced evidence that infants that are born prematurely or whose birth weight is abnormally low for the length of the pregnancy

* NHANES: National Health and Nutrition Examination Survey.
** ISAAC: International Study of Asthma and Allergy in Children.

(so-called ‘dysmature newborns’) are more likely than others to develop asthma symptoms.[95,308-314] Such symptoms are typically observed in the context of respiratory infections. However, other studies have detected no association with asthma symptoms or even an inverse association.[315-319] Some birth cohort studies have found the risk of sensitisation and allergic disorders to be lower among premature infants and higher among high-birth-weight infants and those born after a longer term.[314,320,321] A review published in 2005 concluded that prematurity and low birth weight were risk factors for wheezing in young children, but that it remained unclear whether they were also risk factors for allergic asthma in later childhood and adolescence.[136]

Some asthma symptoms, such as reversible respiratory obstruction and bronchial hyperresponsiveness, can persist into adolescence and depend on the degree of prematurity.[95] A Dutch prospective study of the long-term consequences of prematurity and low birth weight (POPS*) has found that, by the age of nineteen, the prevalences of asthma, wheezing and exercise-induced breathlessness among people born after less than thirty-two weeks gestation or with a birth weight of less than 1500 grams were two to five times as high as in the general population.[322] By contrast, allergy was less common among those who had been premature or dysmature.[314] According to a recent Dutch review, it is still unclear which (immunologic) mechanisms define the relationship between foetal growth and the development of asthma.[323]

5.3.6 *Outdoor air pollution*

In the past, studies into the health effects of outdoor air pollution tended to concentrate mainly on episodes of air pollution (smog); more recently, the focus has shifted to traffic-related air pollution. Research to the effects of other, typically local, sources of air pollution is not considered here, since it does not lend itself to the formulation of general conclusions.

A Dutch cross-sectional study of children living close to busy highways found that chronic respiratory symptoms and lung function abnormalities were associated with the truck traffic intensity and the related levels of air pollution.[324,325] The elevated prevalence of respiratory symptoms was particularly marked among sensitised children and children with bronchial hyperresponsiveness.[326] Investigators in other countries have also reported that children living near to busy roads are apt to suffer more respiratory complaints and asthma than their peers.[327-331] In addition, adults in the Netherlands are more likely to report

* POPS: Project On Preterm and Small for gestational age children.

respiratory complaints if they live on a street where the concentrations of traffic-related air pollution are elevated than if they live in cleaner-air locations.[332] A German study has produced corroborating evidence.[333]

In California, large groups of school children in twelve cities were followed up.[334,335] Children with asthma proved more likely to develop chronic lower respiratory tract symptoms if they were exposed to air pollution.[336] The association was strongest where nitrogen dioxide was concerned, but was apparent with particulates as well. The observed effects were greater than those detected in earlier cross-sectional studies.[337] Negative effects on lung function development were observed in the study cohort at common levels of exposure to various atmospheric pollutants.[338-340] Furthermore, lung function development in children living within 500 metres from a highway was impaired relative to such development in children living at least 1500 metres from a highway.[341] The results of another study – the Inner-City Asthma Study – showed that exposure to concentrations permissible under US air quality rules could lead to a rise in respiratory complaints and diminished lung function in asthmatic children.[342]

In the international prospective TRAPCA study*, a detailed estimate was made of the exposure to various traffic-related air pollutants – nitrogen dioxide, particulates ($PM_{2.5}$**) and soot – of participating children.[343-345] The investigators then analysed the relationship between the estimated exposure levels and the prevalence of respiratory complaints. In the German birth cohort, an association was found only between the estimated traffic-related concentrations of nitrogen dioxide and $PM_{2.5}$ at the infants' birthplace address and coughing without infection in the first year of life; no association between the pollutants and doctor-diagnosed asthma was detected.[346] In the Dutch PIAMA cohort, there were associations in the first four years of life between elevated exposure to traffic-related air pollution and asthmatic complaints (mainly wheezing), doctor-diagnosed asthma and respiratory infections.[347-349] Earlier studies had additionally demonstrated a link to the occurrence of allergic rhinitis.[350-352] A review concluded that the relationship between long-term exposure to traffic-related air pollution and non-allergic respiratory complaints and disorders is more consistent than that between pollution and the development of allergic complaints and disorders.[353] Another review indicated that there was convincing evidence that people with a predisposition to asthma were more likely to develop symptoms when exposed to outdoor air pollution than people without such a predisposition.[354]

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* TRAPCA: Traffic Related Air Pollution on Childhood Asthma.

** $PM_{2.5}$: particles with a median aerodynamic diameter of less than 2.5 μm.

Summer smog (ozone) can also influence the development of asthma. In areas with high ozone concentrations, the risk of developing asthma within five years was more than three times higher for children who played three or more outdoor sports (n=29) than for children who played no sports (n=104).[355] In areas with low ozone concentrations, there was no difference between the two groups. Other atmospheric agents had no influence on the relationship between outdoor sport and the development of asthma. The authors concluded that exposure to ozone in combination with heavy outdoor excercise contributed to the development of asthma in children.

5.3.7 *Indoor air pollution*

The influence of various indoor environmental factors – allergens originating from domestic pets and house dust mites, fungal agents and bacterial endotoxins – has been considered above. However, damp, tobacco smoke and various (other) chemical agents in indoor air can all influence asthma and allergy as well.

Damp in the home

Various cross-sectional-studies have shown that living in damp conditions is associated with higher frequencies of asthmatic complaints in both children and adults.[38,356-362] In one of these studies, an association remained present even after correcting for the concentration of house dust mite allergens.[359]

In a Dutch case-control study, the parents of children with asthmatic complaints were found to be more likely to report signs of mould and damp in the home than other parents.[363,364] People who were sensitised to house dust mites or fungi were also more likely to report signs of damp. A British case-control study revealed a similar association between moisture levels in the home and the seriousness of asthmatic complaints, especially among sensitised individuals.[365] These findings suggest that house dust mites and fungi, which thrive in damp environments, have a causal role in development of asthma and allergy.

Only a few prospective studies have been conducted in this field, however. In a cohort of nearly two thousand Finnish children, a positive association was detected between the presence of mould odour in homes and the incidence of asthma in the first seven years of life.[366] The Swedish BAMSE birth cohort study also established an association between the number of signs of damp in the home and the occurrence of persistent wheezing.[367]

Tobacco smoke

The most significant form of indoor air pollution is tobacco smoke. The Health Council's 2003 report *Volksgezondheidsschade door passief roken* (*The Impact of Passive Smoking on Public Health*) described the results of a number of meta-analyses, indicating that parental (particularly maternal) smoking increases the risk of a child subsequently developing asthma by 20 to 45 per cent.[368] The observed effect was associated with both prenatal exposure and passive exposure in the early years of life.

Nitrogen oxides

Dutch studies into the effects of nitrogen oxides in the home or cooking with gas on the incidence of childhood asthma symptoms revealed little of concern.[369-371] There is some evidence, however, of bronchial hyperreactivity in adults, particularly sensitised adults, in response to exposure.[372,373] Also, several international-birth cohort studies suggest that a cautious approach may be warranted: exposure to nitrogen dioxide appears to increase asthma symptoms in young children, particularly in combination with exposure to tobacco smoke.[374-376] Nitrous acid (HONO) may also play a role.[377,378]

Volatile organic compounds

The association between exposure to volatile organic compounds in the indoor environment and asthma or allergy has so far been investigated only through cross-sectional or case-control studies. The findings of two cross-sectional-studies, one in Finland, the other in Russia, indicate an association between the presence of synthetic wall coverings, (other) new surfacing materials and asthma or allergy, even after correcting for various confounding factors.[379,380] The results of four case-control studies conducted in the UK, Finland, Sweden and Australia were inconclusive, however.[365,381-383] In the USA, a recent large-scale cross-sectional study (NHANES*) revealed an association between personal exposure to volatile organic compounds and doctor-diagnosed asthma and wheezing attacks.[384] In view of the methodological problems that studies of this kind entail, it is likely that prospective studies can shed more light on the issue of whether relatively low common levels of exposure to volatile organic compounds in the home carry a risk of asthma.[385]

* NHANES: National Health and Nutrition Examination Survey.

Chlorine compounds in the air at indoor swimming pools

Belgian investigators have reported an association between swimming in indoor pools and the incidence of asthma symptoms.[386-390] The investigators suggest that chlorine compounds in the air at indoor swimming pools may promote the development of asthma. Their conclusions have been criticised, however, partly on the grounds that not enough was done to correct for possible confounding factors.[391] Nevertheless, the findings have caused some concern – in the Netherlands as well as Belgium – concerning air quality at swimming pools. In the Netherlands, the use of chlorine is compulsory for the disinfection of public swimming pools.[392] On the basis of a literature review, a Dutch research team has concluded that, while it is likely that increased exposure to irritants, including chlorine compounds, can aggravate existing asthma, normal levels of exposure are unlikely to be capable of causing asthma in the first place.

German investigators recently reported the elevated prevalence of hay fever in adults who were frequent swimming pool users, mainly during their school years. The investigators suggested that damage to the respiratory epithelium caused by chlorine compounds might facilitate internal exposure to allergens.[393] On the other hand, Italian investigators have reported that the nitrogen monoxide concentration in the air exhaled by a hundred children who spent one to two hours a week in an indoor swimming pool was no higher than that in the air exhaled by 141 children who were not regular swimming pool users.[394] This research team concluded that intermittent exposure to chlorine compounds did not cause respiratory inflammation, an early symptom of asthma.

The Committee concludes that the evidence for an association between exposure to chlorine compounds and the development of asthma is not sufficiently strong to justify discouraging children from using indoor swimming pools. However, the Committee does believe that the parents of asthmatic children should be informed of the possibility that asthmatic complaints may be aggravated by strong stimuli, such as provided by chlorine compounds.

Other respiratory stimuli

Some people exhibit a hypersensitivity response to exposure to very particular stimuli, i.e. they exhibit objectively reproducible symptoms and phenomena when exposed to the stimuli in question at dosages that most people can tolerate.[24] Exposure to respiratory stimuli usually has a direct irritating effect on the respiratory tract, but may also promote the development and progression of allergic reactions to allergens.[395] Damage to the respiratory epithelium may make it easier for allergens to enter the body.

5.3.8 *Combinations of environmental factors*

The findings of studies into the influence of individual risk factors on the development of asthma and allergy are somewhat equivocal. With the exceptions of passive smoking and sensitisation to house dust mites or domestic pets, no single factor appears to be of exceptional significance. Furthermore, in most cases, the observed effects are not very strong: elevation of the risk by more than a factor of two is unusual. There is also little consistency between study results in different populations. Perhaps, therefore, the attention should be on a combination of risk factors, such as a 'western lifestyle'.[396] However, little research into the effects of combinations of factors has so far been conducted.

The (non-experimental) studies that have looked at combinations of risk factors include cross-sectional studies in Sweden and China, and a prospective study in the USA.[397-400] One of the Swedish cross-sectional studies examined the risk of sensitisation to cat allergens in asthmatic toddlers who were exposed in the home to a combination of cat allergens, parental tobacco smoke and damp phenomena.[397] The presence of all three risk factors was found to increase the risk of sensitisation forty-two times. In a Swedish variant of the ISAAC study*, school children with asthma in the family whose mothers smoked and signs of damp in their homes, were found to be at thirteen times the risk of developing non-allergic asthma.[398] Another revealing example of research into a combination of risk factors is a cross-sectional study carried out in China, which was able to fully attribute a 40 per cent variance in the prevalence of allergic disorders across three cities to a combination of eight diverse factors.[399] The Committee believes that similar designed studies could yield important insights in the Dutch context. Birth cohort studies can also be used to examine the influence of combinations of lifestyle-related and environmental risk factors in the first years of life on subsequent sensitisation and asthma development. In a Californian study, for example, it was established that the effect of air pollution on respiratory complaints was amplified in asthmatic children by contact with dogs.[400] Several relevant clinical trials are considered in section 6.

The contributions made by different environmental factors to the development of asthma or allergy can be expressed in terms of population attributive risk (PAR).[401] To calculate a PAR, one needs to know the relative risk associated with the factor and the proportion of the population who exceed the critical exposure

* ISAAC: International Study of Asthma and Allergy in Children.

level, i.e. whose exposure to the factor in question is sufficiently high to induce effects. PAR data can be useful for the prioritisation of interventions. A review has been published, giving estimated PARs for a number of environmental factors known to influence the development of asthma and allergy in the population of the USA.[402] The authors concluded that only exposure to tobacco smoke and house dust mites played a demonstrable causal role. They additionally identified a number of factors that probably contributed to risk: exposure to allergens from cockroaches, domestic pets and fungi, low birth weight, membership of a small family and exposure to viral infections. The investigators' attributive risk estimates have a considerable range, mainly because there is considerable uncertainty concerning the proportion of the population (and the proportions of the high-risk groups) whose exposure to the relevant risk factors exceed the critical level, and because there is considerable variation in the temporal and spatial distribution of exposure to environmental factors. Any attempt to calculate PARs for the Netherlands would be hampered by a similar paucity of precise data. In view of this fact and the equivocal nature of many of the epidemiological study findings concerning the influence of individual factors, the Committee sees little value in estimating the attributive risks associated with individual environmental factors for the Dutch population. Estimation of the contribution that historical shifts in the levels of exposure to environmental factors have made to changes in the prevalence of asthma and allergy would be even more difficult.

5.4 Conclusions

The development of asthma and allergy is influenced by both genetic and environmental factors. The Committee has not attempted to quantify the associations. The relative risks calculated in different studies are generally too divergent or the confidence intervals too wide to be informative.

Predisposition and the immune system

It has long been recognised that the development of asthma and allergy has a hereditary component: the children of asthmatic or allergic parents are more likely to acquire an allergy or asthma than other children. However, predisposition is not attributable to a single gene, but to a whole series. Large studies would be required in order to identify the genes that, in interaction with environmental factors, determine whether and (if so) when one will develop asthma or allergy.

Environmental factors

More is known about the environmental factors that play a role in the development of asthma and allergy.

Micro-organisms. The influence of infections differs from one group of micro-organisms to the next. A number of studies have suggested that certain gastrointestinal infections reduce the likelihood of subsequently developing allergic disorders. The intestinal flora may play a role in this context. Little is known about the influence of respiratory infections on the development of allergic disorders. However, there is reason to believe that children who exhibit signs of Respiratory Syncytial Virus (RSV) infection early in life are more likely to develop asthma later. There is no evidence of a causal relationship between vaccination or the early use of antibiotics and the development of allergy or asthma.

Microbiological agents. The relationship between exposure to non-infectious microbiological agents, such as bacterial endotoxins, in domestic dust and asthma and allergy is complex. There is evidence that endotoxins inhibit allergic sensitisation, but also that they are associated with the development and aggravation of asthma. Important interactions with particular genes have recently been discovered, suggesting that the relationships between, on the one hand, endotoxins and, on the other, asthma and allergy can vary considerably between people with different genotypes. It is unclear whether endotoxins actually play a causal role, or serve merely as an indirect indicator of exposure to other environmental factors, such as certain fungal agents. The Committee concludes that the extent to which non-allergenic microbiological agents can protect against the development of allergic disorders remains uncertain.

Allergens. Exposure to specific allergens is a prerequisite for the development of the associated allergy. A prospective study in which early exposure to allergens was measured revealed that there is a positive relationship between such exposure to allergens, particularly those from house dust mites and cats, and sensitisation. To date, little evidence has been found to indicate that vermin allergens play a significant role in the Netherlands. Although sensitisation and asthma are related, not enough is yet known about the influence of early allergen exposure on the development of asthma. The contribution of sensitisation to fungal allergens to the development of respiratory tract illnesses remains uncertain. However, the findings of a prospective study indicate that infants with cow’s milk or hen albumen allergies are more likely to develop allergic disorders during their school years.

Breastfeeding. Most of the relevant prospective studies have found that exclusive breastfeeding for at least three to four months tends to protect against

the development of asthma and allergy, particularly in the children of asthmatic or allergic parents. However, some studies looking at the longer-term effects of breastfeeding on the development of asthma and allergy have yielded equivocal results.

Diet. Diet can also influence the development of asthma and allergy. There are indications, for example, that certain components of fruit, vegetables and oily fish may have a protective effect. By contrast, other fats and salt have been reported to have adverse effects.

Overweight. There is evidence that overweight increases the likelihood of developing asthma. The relationship between bodyweight and asthma is complex, however, and there is as yet insufficient evidence to conclude that it is causal.

Prematurity. People who were born prematurely are at increased risk of asthma symptoms and lung function abnormalities throughout their childhood and into adulthood, but there is no proven association between prematurity and allergy. It seems likely that the respiratory symptoms are the result of a different etiologic mechanism from that responsible for allergic asthma.

Outdoor air pollution. Outdoor air pollution, in particular that originating from traffic, can aggravate asthma and other respiratory complaints. It is not yet clear, however, to what extent such pollution also plays a role in the initial development of asthma and allergy.

Indoor air pollution. The most significant form of indoor air pollution is tobacco smoke. The Health Council's 2003 report *Volksgezondheidsschade door passief roken* (*The Impact of Passive Smoking on Public Health*) concludes that parental smoking, particularly smoking by the mother during pregnancy, increases the risk of the child subsequently developing asthma by 20 to 45 per cent.[368] Since the publication of that report, no study results have been published which might call this conclusion into question. Various studies have also demonstrated a relationship between living in a damp home and the risk of asthma or allergy. However, it is not yet clear whether damp is primarily an indirect indicator of exposure to mite or fungal allergens or whether other factors in indoor air are responsible for the observed effects. In the Committee's view, there is presently insufficient evidence to conclude that using indoor swimming pools influences the development of asthma.

To sum up: various environmental and lifestyle factors, sometimes in interaction with genetic factors, play significant roles in the development of asthma and allergy. Given that changes in the genetic makeup of the population are inherently gradual, changes in the prevalence of asthma and allergy – besides changes

attributable to developments in diagnostic practice – are probably due primarily to changes in environmental and lifestyle factors. However, it is not yet clear which factors contribute, and to what extent.

Chapter 6

The effectiveness environmental control measures

In this section, the Committee addresses the State Secretary's last request, which concerned ways of reducing asthma and allergy:

> Can the Health Council indicate what environmental control measures are likely to be most effective – for the various high-risk groups and in the various phases of life – both as means of preventing the initial development of asthma and other respiratory allergies and as means of improving the condition of asthma and respiratory allergy patients by reducing their complaints?

In responding to this request, the Committee has confined itself to the effects of environmental control measures for the (primary* and tertiary**) prevention of asthma and allergy. The effectiveness of medicinal treatments for asthma and allergic disorders, such as bronchodilators, inhalant corticosteroids and immunotherapy, is outside the scope of this report.

For its assessment of the effectiveness of the different interventions, the Committee has weighted the available evidence in accordance with the recommendations of the Dutch Cochrane Centre, the Dutch Institute for Healthcare Improvement and other bodies, as follows[403]:

* Primary prevention entails preventing new cases of an illness – in the broadest sense of the word – by removing its cause or causes.

** Tertiary prevention involves preventing the aggravation of an illness that the patient already has.

- systematic reviews of randomised, controlled clinical trials
- randomised, controlled clinical trials (RCTs)*
- non-randomised, controlled clinical trials (e.g. cohort studies)
- non-controlled studies.

The Committee has therefore looked first at systematic reviews and meta-analyses of clinical trials of environmental control measures considered capable of influencing the course of asthma and allergy, such as those supported by the Cochrane Collaboration**. Most of the available publications of this kind are Cochrane reviews of studies into the effects of control measures on the prevalence of asthma or allergy complaints.[404-412] The measures in question mainly involved the reduction of concentrations of allergens from house dust mites and domestic pets in the homes of sensitised individuals. The results are discussed in subsection 6.1. More recent clinical trials have tended to focus on the primary prevention of asthma or allergy; such prevention is considered in subsection 6.2. The Committee's conclusions are presented in subsection 6.3.

6.1 Control measures for the reduction of complaints

In the past, various study reports have been published, describing how people with allergic asthma experienced considerable relief as a result of spending time in a 'dust-free' room or in the mountains, where house dust mites find it very difficult to survive.[413-416] Encouraged by these reports, there used to be considerable optimism regarding the potential health benefits attainable by intervening to control individual risk factors. The findings of the earlier reports have been confirmed more recently by studies of asthmatics who spent time in the Alps.[417-420] Since then, various studies have been carried out to determine whether similar benefits could be secured by reducing allergen exposure in the home environment. In the interpretation of the results of these studies, relatively little attention has been given to the effect of the personal supervision on the health of study subjects.

* Randomised, controlled clinical trials: studies in which one randomised group (i.e. a number of people selected at random) is subject to an intervention whose effectiveness is under examination, while another group is subjected to an ineffective intervention that is superficially indistinguishable from the potentially effective intervention (placebo); such trials are often 'double blind', which means that neither the researchers nor the subjects know which intervention a given individual is receiving.

** Cochrane Collaboration: an international non-profit organisation that encourages and supports the performance, maintenance and distribution of systematic reviews.

6.1.1 *Clinical trials in the Netherlands*

Reduction of house dust mite allergens

In a randomised, double-blind, placebo-controlled trial, thirty asthmatics of between eleven and forty-four years old were studied to determine the effect of using of anti-allergic mattress covers.[421,422] After a year of using the covers, the house dust mite allergen concentrations in the mattress dust of asthmatics sleeping in rooms without fitted carpets showed a statistically significant reduction of up to 10 per cent of the starting value. However, the subjects with moderate to serious asthma did not experience any improvement in bronchial hyperresponsiveness and/or asthmatic complaints, and there was no change in the usage of asthma medication.

In the SGO allergy study*, 325 allergic individuals between eight and fifty years old were studied. Some 279 of them suffered from rhinitis, 167 from asthma and eighty-six from atopic eczema. Subjects were provided with allergen-impermeable encasings for mattresses, duvets and pillows** to use for twelve months, on a placebo-controlled basis. The concentrations of house dust mite allergens in subjects' mattress dust fell to 30 per cent of their previous level, but there was no improvement in the condition of the allergic rhinitis or eczema patients.[423,424] Even when the asthma, rhinitis and eczema patients sensitised to house dust mites were treated as a single group in the analysis and assessed using a non-specific outcome index (SF36***), no evidence could be found that the allergen-proof bedding had any beneficial effect.[425]

The double-blind, placebo-controlled Preventum study in Maastricht involved fifty-two adults with a mild form of asthma**** combined with a house dust mite allergy. This study found evidence that impermeable mattress covers had a slight beneficial effect on both house dust mite concentrations and lung-function.[426] The number of subjects was small, however, and the intervention period just nine weeks.

In the IBA study*****, seventy-six people with mild asthma submitted to an intervention intended to reduce their exposure to house dust mites for twenty

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* SGO: Stimulering GezondheidsOnderzoek (Health Research Promotion).

** Subjects were allowed to take action to reduce their exposure to inhalation allergens during the intervention period, e.g. by cleaning, airing and washing bedding; however, they were not allowed to make any modifications to their homes, such as changing their floor coverings.

*** SF36: short form with thirty-six questions.

**** without the use of inhalant corticosteroids

***** Interaction Bronchodilatation and Allergen exposure.

weeks. The investigators were not able to observe any change in bronchial hyperresponsiveness, lung function or asthma symptoms relative to a placebo group.[427,428]

Administration of probiotics*

In a randomised double-blind placebo-controlled trial in the Netherlands, infants (less than five months old) with atopic eczema were given Lactobacillus rhamnosus (n=17), Lactobacillus GG (n=16) or a placebo (n=17) for three months.[429] The clinical seriousness of their eczema was evaluated before, during and after the intervention. Total IgE and food-specific IgE were measured, as were a number of inflammation parameters. The administration of probiotics was not found to have any statistically significant effect on eczema, IgE status or inflammation parameters.

6.1.2 Clinical trials in other countries

A number of Cochrane reviews have been published, examining the effectiveness of specific environmental control measures.[404-412] Effectiveness was evaluated in relation to individual environmental factors; most of the studies involved forms of intervention that were aimed at a single environmental factor. In the following paragraphs, the Committee considers these reviews and the large-scale Inner-City Asthma Study. The latter was not yet covered by the Cochrane evaluations, and involved intervention aimed at several environmental factors.[430]

Reduction of house dust mite allergens

According to several Cochrane reviews, published between 1998 and 2004, measures aimed at reducing the concentration of house dust mite allergens to which people allergic to the mite are exposed did not bring about any improvement in the clinical condition of the asthma and allergy patients involved, who numbered 2,733 in total.[404,405,411] Another review, which focused on the effect of intervention on bronchial hyperresponsiveness, confirmed this finding.[431] The only positive effect attributed to house dust mite allergen reduction was on levels of sensitisation and respiratory complaints in infants.[432]

A Cochrane review of the effect of intervention on asthma symptoms found that in thirteen of the forty-nine clinical trials reviewed, a demonstrable reduction in domestic dust mites or house dust mite allergens was achieved.[411] In all the

* Probiotics are living bacteria administered in food, which are capable of entering the intestines and thus exerting a beneficial influence.

reviewed studies, subjects' allergic status was ascertained by skin prick testing or IgE analysis. Asthma symptoms, asthma medication use and the lung function were used as outcome indicators. The concentrations of allergens were in most cases high enough to constitute a hazard for sensitised subjects, but the levels varied considerably, both from study to study and within the studies. The authors considered it unlikely that, where no effect was observed, this was due to the baseline concentrations of house dust mite allergens being relatively low.

Another Cochrane review looked at four studies that had sought to characterise the effect of house dust mite reduction on the occurrence of allergic rhinitis.[405] In all the studies, reduced concentrations of house dust mite allergens were achieved and rhinitis symptoms declined. The reviewers were of the opinion, however, that the benefits secured were too small and strength of the evidence too weak to support firm conclusions.

Studies involving adult subjects with atopic eczema has yielded contradictory results. A team of German investigators observed no reduction in the seriousness of the subjects' eczema complaints as a result of using allergen-impermeable mattress covers and other house dust mite control measures.[433] Yet, in a Swedish study, the use of impermeable mattress covers *was* found to alleviate subjects' eczema.[434]

Reduction of domestic pet allergens

A 2003 Cochrane review identified only two clinical trials, which sought to characterise the effect of reducing domestic pet allergen concentrations on people who were allergic to pets, and which met the reviewers' selection criteria.[406] In both cases, intervention took the form of air filtration using a HEPA* filter. Neither study revealed any effect on lung function or on coughing. However, the studies were too small to support any firm conclusion regarding the value of using a HEPA filter. In a more recent, small-scale, non-randomised, non-blind, prospective study, twenty new asthmatics with domestic pet allergies were followed up after being advised to stop keeping pets.[435] The progress of these subjects' disorder was compared with that of asthmatics in a reference group, who had continued to keep pets. After a year, a statistically significant reduction was recorded in the levels of bronchial hyperresponsiveness in the intervention group.

* HEPA: High Efficiency Particulate Air.

Reduction of food allergens

One small clinical trial has provided evidence that the seriousness of atopic eczema in infants can be reduced by a hypoallergenic maternal diet during breastfeeding.[436] However, more research is considered necessary before definitive conclusions can be drawn regarding the efficacy of a hypoallergenic maternal diet during breastfeeding.

Administration of probiotics

In Finland, a double-blind randomised placebo-controlled trial was performed to study the effect of dietary probiotics on atopic eczema in infants.[437] Half of the study group of twenty-seven breastfed infants with atopic eczema were switched to a diet of infant formula with added probiotics (in particular Lactobacillus GG). After two months, a statistically significant improvement was observed in the skin disorders of subjects in the intervention group, compared with the control group. However, a recent review concluded that there was as yet little evidence that probiotics were beneficial.[438] This conclusion was based partly on the fact that probiotics have not been shown to have any influence on objective indicators of allergy such as the IgE status or skin prick test results.

Diet

According to another Cochrane review, dietary changes, such as consuming more fish oil, have no effect on asthmatic complaints.[412] The reviewers also concluded that it had not been convincingly demonstrated that reducing salt intake could reduce asthma symptoms.[409]

Reduction of traffic-related air pollution

The introduction of a new traffic management system in Atlanta during the 1996 Olympic Games for congestion control purposes provided an opportunity to study the health effects of a brief change in air pollution levels.[439] For the duration of the games, traffic density and the atmospheric concentrations of particulates and ozone were significantly lower than in the month before the games or in the month after. During this period, there was also a statistically significant reduction in the number of asthma-related emergency hospital admissions.

Use of ionisers

The efficacy of using ionisers (mobile air purifiers) was considered in a Cochrane review published in 2003.[408] On the basis of six randomised trials involving 106 subjects, it was concluded that ionisers had no statistically significant positive effect on asthmatics' lung function, complaints or medication use.

‘Healthy’ homes

The effectiveness of improved domestic ventilation as a means of alleviating asthma and allergic disorders has been investigated in a number of small-scale trials.

In a Danish non-randomised trial, thirty asthmatics were monitored after moving to homes with mechanical ventilation systems and heat exchangers, where the levels of damp and the concentrations of house dust mite allergens were demonstrably lower than their old homes.[440] Fourteen asthmatics with house dust mite allergies recorded a statistically significant reduction in medication use following the move.[441] Improvements in lung function and asthmatic complaints were also observed. A Finnish prospective cohort study followed asthmatics who were offered ‘healthy’ homes in a new apartment complex with good mechanical ventilation (air extraction and refreshment), where the indoor air was generally less polluted than in another new apartment complex.[442] In the first year, fewer asthmatic complaints were reported by the subjects, particularly in cases where the circulation rate* was increased. In the Netherlands, there has also been a study of asthmatics who moved to new ‘low-allergen’ homes with higher-capacity mechanical ventilation and extraction systems, but the results have not yet been published in a peer-reviewed journal.[443] Because it is impossible to blind studies of this kind, or to separately evaluate the many potentially significant changes that moving home entails, the evidence provided by the studies described above is not strong enough to support practical conclusions.

In a randomised, controlled British trial, the installation of mechanical ventilation systems providing air extraction and refreshment and heat exchangers in the existing homes of forty asthmatics with house dust mite allergies resulted in a statistically significant reduction in bedroom carpet allergen concentrations and a trend towards improved bronchial hyperresponsiveness, but not in any alleviation of respiratory complaints.[444] The study was, however, too small to support any statistically valid conclusions regarding the health effects of the changes.

Multi-factor reduction

In a large-scale randomised, controlled clinical trial involving 937 children with allergic asthma in seven large US cities (the Inner-City Asthma Study), a special package of measures was devised for each child, depending on his or her allergic status. These measures addressed the particular risk factors in the child’s home environment and involved, for example, reducing exposure to inhalation allergens and tobacco smoke.[430] In the year that the measures were implemented and

* Circulation rate: a figure indicating the number of times per hour the room is supplied with fresh air.

the following year, children in the intervention group suffered from asthmatic complaints less often than those in the control group (3.4 days every two weeks, as opposed to 4.2). A statistically demonstrable association was found between the reduction in cockroach and house dust mite allergen concentrations and the reduction in asthmatic complaints. Partly on the basis of these findings, the authors of a 2005 review concluded that a broad package of control measures aimed at reducing exposure to several environmental factors at once seemed likely to reduce asthmatics' complaints.[445]

6.2 Control measures to prevent asthma and allergy

In the early 1990s, it was suspected that asthma and allergy could be prevented to some degree by drastically reducing exposure to allergens.[446-448] The 1992 Health Council report *Allergie, CARA en allergenen in woningen* (*Allergy, Asthma, COPD and Allergens in the Home*) stated that, while it was probable that allergen avoidance in the first two years of life could prevent susceptible children developing allergy and possibly asthma, little research had been conducted into the possibility.[449] The committee responsible for the report therefore recommended a combination of cohort studies and clinical trials involving the children of allergic or asthmatic parents, mainly with a view to clarifying the quantitative significance and duration of the sensitive period. In the Netherlands and elsewhere, numerous prospective clinical trials have since been started in order to study the influence of strategies such as allergen avoidance on the development of asthma and allergy in children.[450,451] In addition to those that have focused on mono-factor control measures, there have been studies into the efficacy of multi-factor control measures aimed at reducing exposure to both inhalation allergens and food allergens. Because many of these long-term studies are still in progress, it is not yet possible to reach any definitive conclusions regarding their findings.

6.2.1 Clinical trials in the Netherlands

PIAMA study*

In the PIAMA birth cohort study, 4,146 children have been followed up from birth.[452] PIAMA is a prospective study concerned with various risk factors for asthma and allergy: house dust mites, domestic pets, damp in the home, breast-feeding and diet and air pollution. From this group, 855 children with allergic mothers were selected to take part in a double-blind, randomised, placebo-con-

* PIAMA: Prevention and Incidence of Asthma and Mite Allergy.

trolled clinical trial designed to study the effect of allergen-impermeable covers for mattresses and pillows for suppressing house dust mite allergens. During the last three months of pregnancy, allergen-impermeable and placebo covers were given out for use by both parents and children.

In the first few years, the impermeable mattress covers had a minor beneficial effect on the amounts of dust and allergens in the mattresses.[453] After a year, the concentration of house dust mite allergens in the mattresses was halved. After two years, there was a statistically significant effect on reported night-time coughing, but no effect on sensitisation.[454] Although subjects made use of the impermeable mattress covers as advised, after four years the effects on both Der p1* concentrations and on symptoms had worn off .[455] The concentration Der f1** remained lower in the intervention group, however.

When interpreting the results summarised above, it is important to bear in mind that the study started shortly after the second of two very cold winters (1995/1996 and 1996/1997). It is likely that, because the cold had already significantly reduced mite allergen concentrations, the further exposure reduction brought about by use of the impermeable mattress covers was too small to have any clinical effect.[456,457] It is not therefore possible to conclude from the study findings that anti-allergic mattress covers are ineffective as a means of preventing allergy and asthma.

PREVASK study***

In the PREVASK study, 843 children – 535 of whom have an asthmatic family member – have been followed up from birth.[458] Of this high-risk group, 434 children participated in a randomised, controlled clinical trial.[217] A specially trained nurse visited each participating family three times and gave practical advice, e.g. that the babies should be exclusively breastfed in the first months and that exposure to tobacco smoke and allergens from house dust mites, domestic pets and food should be minimised****. The control group received the usual support, in

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* Der p1: Dermatophagoides pteronyssinus, a common species of house dust mite in Europe.

** Der f1: Dermatophagoides farinae, a common species of house dust mite in Europe.

*** PREVASK: Prevention of Asthma in Children.

**** PREVASK intervention programme:
1 Avoidance of exposure to tobacco smoke: parents advised to prevent antenatal and perinatal passive smoking
2 Avoidance of exposure to house dust mite allergens from birth: smooth floor coverings, thorough floor cleaning, washing bedding at 60 degrees, use of house dust mite-proof covers, continuous ventilation and daily airing for an hour
3 Avoidance of exposure to domestic pet allergens from birth: no cats or dogs in the house
4 Avoidance of exposure to food allergens the first six months: exclusive breastfeeding or, where necessary, hydrolysed formula feeding (infant formula containing hydrolysed protein instead of intact cow's milk protein).

accordance with the NHG* standard. So far, the effects of the intervention programme during the first two years of life have been published.

In the group that received the special advice, a strong reduction was observed in the average amounts of house dust mite allergens and domestic pet allergens found in samples taken from the impermeable mattress covers.[459] The amount of house dust mite allergens found in dust samples from the living rooms was also lower. It is worth noting that there was a clear decline in cat allergens in control group homes as well. By the time the children had reached the age of two, the effect of the intervention was a modest but statistically significant decline in the frequency of asthmatic complaints (wheezing, breathlessness and night-time coughing), as reported by the parents.[217] The greatest protective effect was associated with a low concentration of house dust mite allergens, followed by maternal non-smoking and breastfeeding for more than one week. Because it was not possible to 'blind' the participants, the possibility cannot be excluded that the parents' reporting of complaints was influenced by awareness of the intervention. Nevertheless, the investigators have used their findings to argue for a multifactor approach to environmental control: the promotion of a package of control measures that are relatively straightforward to implement in the context of the Dutch health care system.

BOKAAL study**

The BOKAAL study is a double-blind, randomised, placebo-controlled clinical dietary trial involving 1,108 breastfed infants.[460,461] The intervention involved giving newborn subjects infant formula containing cow's milk protein for three days and then exclusive breastfeeding for at least three months. The infants in the intervention group were compared with infants who were exclusively breastfed for the first three months of life. The hypothesis was that the intervention would induce tolerance to cow's milk. However, this early and brief exposure to cow's milk had no discernible effect on the prevalence of cow's milk allergy or other allergic disorders among the study group at the age of five years.

INDIAAN study***

The ongoing INDIAAN study is investigating whether inoculating children of various ages with a tuberculosis vaccine (BCG) modulates the immune system so as to make the development of asthma or allergy less likely. Although this proce-

* NHG: Netherlands Association of General Practitioners.
** BOKAAL: Alternation of Breastfeeding and Cow's Milk: Allergy?
*** INDIAAN study: Indirect Infection Allergy and Asthma-Neutralisation study.

dure has been shown to have positive effects in laboratory animals, it is not yet clear whether it can also be beneficial to people.

KAMEEL study*

Experiments with laboratory animals have yielded evidence suggesting that the addition of probiotics to infant formula can inhibit the development allergic disorders.[462] Following on from a similar Finnish study, investigators in Rotterdam are presently conducting the 'KAMEEL study', which aims to shed light on the effect of probiotic administration on the development of allergic disorders in infants.

6.2.2 *Clinical trials in other countries*

Isle of Wight study

The 1990 Isle of Wight study, in which 120 children were followed up from birth, was the first attempt to scientifically characterise the effects of primary preventive measures.[463] Subjects were selected on the criterion that both parents were sensitised and that the infant exhibited an elevated umbilical cord blood IgE level. In the randomised intervention group of fifty-eight children, not only were steps taken to reduce exposure to house dust mites (such as the application of insecticide to the floor coverings), but dietary advice was also given. This advice included asking the mothers either to breastfeed for the first year and not to give their babies anything which might trigger an allergic response, or to feed their babies a hydrolysed formula** so as to avoid exposure to cow's milk protein.

In the first year, there was a statistically significant reduction in the prevalence of eczema and asthma in the intervention group.[463] After two years, the intervention group displayed fewer allergic symptoms, but the differences in asthma prevalence were no longer statistically significant. At that age, the intervention group was, however, less likely to be sensitised to respiratory or dietary allergens than the control group. By the age of eight, allergic sensitisation, bronchial hyperresponsiveness and asthma symptoms were all still significantly less common in the intervention group.[463,464]

Manchester Asthma and Allergy Study (MAAS)

In the Manchester Asthma and Allergy Study, 291 children at elevated risk (both parents atopic) were followed up from birth.[465] The subjects were randomly

* KAMEEL: Cow's Milk Allergy with Elimination and Lactobacilli.
** Hydrolysed infant formula: infant formula containing hydrolysed protein instead of intact cow's milk protein.

divided into two equal groups before birth, and a variety of allergen suppression measures made available to the parents of one group. From the fourth month of the pregnancy, for example, the intervention-group parents slept on new mattresses with house dust mite-impermeable covers for mattresses, duvets and pillows. All infants made use of similar bedding from birth. Bed linen was washed every three days at sixty degrees. In the rest of the home, the carpets and other floor coverings and the sofas and chairs were treated with an insecticide. Intervention-group parents were also provided with an extra-powerful vacuum cleaner and a vinyl floor covering was laid in the baby room. None of these interventions were implemented in the control group.

After a year, in the intervention group the house dust mite allergen levels in the mothers' mattresses had been reduced by nearly 98 per cent. On the subjects' bedroom floors, the average house dust mite allergen levels were nearly 30 per cent lower. The prevalences of wheezing and (night-time) coughing were lower in the children by the age of one year, and they were less likely to be prescribed medication for wheezing.[465,466] By this age, however, the intervention group exhibited more sensitisation (positive skin prick test results), although the difference was not statistically significant. By the age of three, the intervention group exhibited better lung function, but also a statistically significant higher prevalence of sensitisation than the control group.[467] The fact that the number of respiratory complaints nevertheless fell was attributed by the authors to reduced allergen exposure. They suggested that the higher prevalence of sensitisation was due to children who were unused to house dust mite allergens (because of growing up in a low-allergen environment) occasionally being exposed to higher concentrations of such allergens. However, the house dust mite reduction measures did not ultimately result in the desired reduction in allergic symptoms.

Childhood Asthma Prevention Study (CAPS)

In Australia, 616 children with a family anamnesis of asthma were followed up from birth.[468] The children were randomly divided into groups before birth. The double-blind intervention involved, on the one hand, the provision of house dust mite reduction measures and, on the other, dietary supplementation of fish oil plus rapeseed oil, rich in 'omega-3' or 'n-3' fatty acids, or a placebo. The dietary supplementation began either when formula feeding began, or after six months of breastfeeding.

A statistically significant lower prevalence of sensitisation was observed in children in the house dust mite intervention group at the age of three years.[468] In the dietary intervention group there was a statistically significant reduction of 10 per cent in coughing complaints only among children whose skin prick tests

were positive. At the age of five, 516 of the 616 children were evaluated.[469] The house dust mite reduction measures were found to have brought about a 61 per cent reduction in the concentration of house dust mite allergens, but there was no difference between the reduction-measure intervention group and the control group in terms of the prevalence of asthma, wheezing or sensitisation. The ratio of omega-6 and omega-3 fatty acids in the plasma of dietary intervention group subjects was lower, but the prevalences of asthma, wheezing, eczema and sensitisation were the same as in the control group.

Canadian Childhood Asthma Primary Prevention Study

In a randomised controlled clinical trial, 545 Canadian children with an asthmatic or allergic family member were divided into an intervention group and a control group. Various measures were taken before birth and in the first year of life to reduce exposure to respiratory and food allergens in the intervention group.

After two years, the concentrations of house dust mite allergens were found to be reduced in intervention group subjects' mattresses, but not on the floors.[470] In households where a cat was no longer kept, the concentrations of cat allergens were also reduced. Most families followed the advice not to keep domestic pets, but not all. When the subjects were two years old, there was a modest but statistically significant reduction in the prevalence of asthma symptoms in the intervention group, but there was no difference between the groups in terms of the prevalence of sensitisation.[471,472] By the time the subjects had reached the age of seven, the prevalence of asthma, as diagnosed by a paediatric allergologist, in the intervention group remained statistically significant lower than in the control group.[473] The investigators concluded that, in this population, the reduction of exposure in the first year of life was effective as a means of preventing asthma.[472]

Study on the Prevention of Allergy in Children in Europe (SPACE)

In the SPACE study, 696 children of allergic parents in five European countries have been followed up from birth.[474] The allergen control measures included the use of allergen-impermeable mattress covers and the provision of advice on diminishing exposure to food allergens.

The percentage of children found to be sensitised to respiratory or food allergens after one year was lower in the intervention group than in the control group.[474-476] By the age of two, however, there was no longer any difference between the groups.[477]

Reduction of food allergens

On the basis of the results of a number of clinical trials, a Cochrane review published in 2006 has concluded that there is no evidence that a hypoallergenic maternal diet during pregnancy has any positive effect on the incidence of atopic eczema in children up to the age of eighteen months.[436] Insufficient data have been published on the development of other allergic disorders to support any conclusion. It has been observed, however, that following a hypoallergenic diet during pregnancy can lead to malnutrition in both the mother and the unborn child. More research is needed before any definitive statement can be made concerning the efficacy of following a hypoallergenic diet when breastfeeding.

In 2002, on the basis of the findings of six clinical trials that had examined the effect of cow's milk protein avoidance on the development of asthma or wheezing in the first year of life, a team of Cochrane reviewers advised that infants should not be given cow's milk products for at least the first four months if one or more immediate family members has an allergy.[478] The report is endorsed by the Paediatric Section of the European Academy of Allergology and Clinical Immunology (EAACI), which also advises that high-risk children should not be given solids for four to six months.[280] Others take the view, however, that insufficient data are available concerning the effects of food allergen avoidance in infants for the purpose of allergy prevention.[479] The value of hydrolysed infant formula* remains a matter of particular disagreement. A 2006 Cochrane review concluded that, while some studies had produced evidence suggesting that this hypoallergenic infant food reduced the likelihood of asthma and eczema in children with a high allergy risk, there was no reason to believe that for other children it was preferable to exclusive breastfeeding.[480] The Committee shares this conclusion.

Probiotics studies

In Finland, a double-blind randomised placebo-controlled clinical trial has been organised to study the effect of probiotics.[481] Probiotic or placebo dietary supplements were given to 159 pregnant mothers with a family history of allergy, starting four weeks before they were due to give birth. Corresponding dietary supplements were then given to the infants for the first six months of life. Up to the age of two years, the children in the intervention group proved 50 per cent less likely to develop atopic eczema.[481,482] At the ages of four and seven years, the rates of atopic eczema reported in the intervention group remained lower than in the control group.[483,484] No statistically significant differences between the two

* Hydrolysed infant formula: infant formula containing hydrolysed protein instead of intact cow's milk protein.

groups were detected in terms of skin prick test results, allergic rhinitis or asthma. With these and other study findings in mind, two reviews published in 2004 and 2005 suggested that modifying the intestinal flora from birth by introducing micro-organisms or microbiological agents has considerable potential as a means of preventing allergic disorders.[441,485] More recently, however, data have become available from a new clinical trial, which was unable to reproduce the Finnish findings. Indeed, in the new trial, infants who had been given probiotics for the first six months of life exhibited elevated levels of allergic sensitisation at the age of twelve months.[486] The Committee takes the view that the available study data are too inconsistent to conclude that probiotics inhibit the development of allergic disorders.

Multi-factor environmental intervention

The most effective primary means of preventing atopic eczema and asthma in young children is intervention aimed at a combination of environmental factors, including exposure to tobacco smoke.[281,282,487] The best combinations of control measures for the various high-risk groups and extent to which the window of opportunity is restricted to the first year of life remain uncertain.[488]

The results were recently published of a meta-analysis of the effects of mono-factor and multi-factor interventions, as performed in the context of ten published clinical trials. The trials in question involved birth cohorts consisting of approximately 3,500 children who were studied at the ages of two to eight years.[489] The results suggest that less asthma is diagnosed following multi-factor interventions. Mono-factor interventions did not apparently have a similar protective effect. The Committee would add that the various studies differed in terms of the combinations of interventions used, and in terms of the effectiveness of the exposure reduction, and do not therefore support practical conclusions.

6.3 Conclusions

Do control measures reduce asthma and allergy complaints?

Some years ago, several studies yielded evidence that a substantial reduction in exposure to house dust mite allergens could bring considerable relief for asthmatics with a house dust mite allergy. Such studies typically involved subjects being admitted to asthma centres in the high mountains, where house dust mites are very rare. Since the publication of these findings, various studies have been performed with a view to establishing whether similar results could be obtained by reducing exposure to allergens in asthmatics' own homes.

House dust mites. Numerous randomised controlled clinical trials involving allergy patients have demonstrated that the use of house dust mite allergen-impermeable mattress covers can reduce exposure to house dust mite allergens. The exposure reductions did not, however, bring about any improvement in the health of adult asthma or allergy patients. Dutch investigators have also found that the use of impermeable mattress covers by asthma and allergy patients has some effect on allergen exposure levels, but barely any effect on the prevalence of asthma and rhinitis complaints.

Domestic pets. The most obvious way of reducing exposure to domestic pet allergens is the avoidance of contact with animals of the kind that the individual is allergic to. However, the efficacy of such an approach has only been studied in a few good clinical trials, partly because there is no way of blinding such a trial. One small study has nevertheless found that people with pet allergy-related asthma do benefit from ceasing to keep household pets. Modest studies of the efficacy of using HEPA* filters to reduce exposure to domestic pet allergens have provided little evidence to suggest that such filters may be useful as a means of alleviating asthma and allergy complaints. No systematic research has been conducted into the effectiveness of regular pet washing or of keeping pets out of the bedroom or living room.

Hypoallergenic diet. There is no evidence that a hypoallergenic maternal diet during breastfeeding has any positive effect on the seriousness of atopic eczema. The Committee would like to see more research conducted in this field.

'Healthy' homes. A handful of small-scale studies in Denmark and Finland have suggested that moving to a 'healthy' home with a balanced ventilation system can reduce the incidence of asthmatic complaints. Because it is impossible to blind studies of this kind, or to separately evaluate the many potentially significant changes that moving home entails, the evidence provided by the studies described above is not strong enough to support practical conclusions. It is nevertheless worth noting that a Dutch cross-sectional study has demonstrated that in mechanically ventilated homes the concentration of house dust mite allergens in mattress dust is less than half what one typically finds in naturally ventilated homes.

The Committee concludes that the clinical efficacy of interventions that involve changing one particular factor in the environment of asthma and allergy patients has thus far proved marginal. Nevertheless, the results of earlier studies into the effects of substantial allergen avoidance persuade the Committee that, in princi-

* HEPA: high-efficiency particulate air.

ple, comprehensive environmental interventions can be beneficial. Asthma in particular is a multi-factorial disease, and it is therefore likely that the associated disease burden can be significantly alleviated only by multi-factor intervention programmes. Unfortunately, however, such programmes are difficult both to implement and to study. The results of the US Inner-City Asthma Study – in which individualised multi-factor intervention was employed to limit exposure to allergens and tobacco smoke and targeted behavioural support was provided – afford particular support to the idea that bespoke intervention can be beneficial. The Committee would like to see more research conducted in this field.

Do control measures prevent the initial development of asthma and allergy?

House dust mites and domestic pets. The first randomised and placebo-controlled clinical trials indicate that reducing antenatal and neonatal exposure to house dust mite and domestic pet allergens reduces the likelihood of children with a predisposition subsequently developing asthma or allergy. Minimising exposure in the first year of life appears to be particularly effective. However, the study data presently available are somewhat equivocal. A recent British study suggests that the drastic reduction of exposure to allergens can actually amplify sensitisation to house dust mites.

Maternal and neonatal diet. Clinical trials have yielded no evidence that a hypoallergenic maternal diet during pregnancy has any positive effect on the incidence of atopic eczema in infants up to the age of eighteen months. Few data are currently available regarding the efficacy of food allergen avoidance in infancy as a means of preventing allergic disorders. Furthermore, it has yet to be convincingly demonstrated that probiotic supplementation of the antenatal maternal diet can reduce the likelihood of a child developing asthma or allergy.

Breastfeeding. Prospective studies have shown that exclusive breastfeeding for at least the first three to four months reduces the risk of sensitisation, atopic eczema and asthma in the early years of life.

Multi-factor intervention. Early results from several clinical trials lead the Committee to believe that multi-factor intervention (intervening to influence several environmental factors at the same time) with the object of limiting exposure to relevant harmful agents is likely to be a more effective way of preventing asthma and allergy than mono-factor intervention. Multi-factor intervention might typically address environmental factors such as tobacco smoke, allergens, breastfeeding and diet. Differences between the studies so far conducted, in terms of the nature of the interventions and the effectiveness of the individual

interventions, make it difficult to draw definitive conclusions as to which control measures are likely to form the most promising combinations.

Chapter 7

Recommendations

7.1 Practical recommendations

The dissemination of information about the effectiveness of environmental control measures as a means of alleviating complaints or preventing the development of asthma and allergy is primarily a task of care practitioners in, respectively, the curative and preventive care sectors, particularly GPs, pneumonologists, paediatricians and municipal health service staff. Patients' organisations and other community groups also play influential roles. The Committee therefore considers it important that the following recommendations are made known to all concerned.

7.1.1 The use of environmental control measures to alleviate complaints

Numerous environmental factors are known to have a direct aggravating effect on established asthmatic or allergic disorders. Reducing exposure to stimuli or allergens would therefore seem the obvious way of alleviating complaints and improving quality of life. However, the effectiveness of such measures has not in all cases been scientifically demonstrated, partly because such complaints are typically influenced by several factors and partly because major reductions in exposure cannot always be achieved in the context of the everyday environment.

Mono-factor intervention. On the basis of several Cochrane reviews, the Committee concludes that, on its own, the use of house dust mite-impermeable

mattress covers and bedding does little to alleviate asthma or allergic rhinitis complaints. The removal from the home of domestic pets of the relevant kind would seem an obvious solution for anyone who is allergic to pet allergens, although there is little reliable evidence that such action is indeed effective. Studies into the efficacy of special air filters designed to reduce exposure to domestic pet allergens has not yielded sufficient evidence to persuade the Committee that their use is advisable. Nor do the published study findings suggest that improved domestic ventilation should be recommended as a means of alleviating asthmatic and allergic complaints. There is reason to believe, however, that a hypoallergenic maternal diet when breastfeeding can have a positive effect on the seriousness of atopic eczema. The Committee wishes to see further research conducted in this field.

Multi-factor intervention. There is evidence that the simultaneous implementation of a wide range of bespoke environmental control measures aimed at particular risk factors can be effective as a means of reducing asthmatic complaints in children. Exposure to tobacco smoke and specific allergens could be reduced, for example, through targeted lifestyle support. Most of the evidence in support of multi-factor intervention published to date has come from the USA, and it cannot be assumed that the packages of measures used there would be equally effective in the Netherlands. Insufficient study data are available to enable the Committee to judge the effectiveness of multi-factor intervention as a means of helping adults. The Committee notes that several clinical trials are currently in progress, in which either combinations of control measures or control measures for the assistance of very specific patient groups are being assessed, and there is reason to be hopeful that these forms of intervention will prove more effective than those tried in the past.

7.1.2 *The use of control measures to prevent asthma and allergy*

Primary preventive measures are measures intended to prevent the initial development of asthma or allergy. The clinical trial data currently available are in many cases insufficient to provide a basis for practical recommendations.

Probiotics. Finnish research has suggested that intestinal flora may play a role in the prevention of atopic eczema. The antenatal administration of probiotics to expectant mothers with a family history of allergic disorders and the neonatal administration of probiotics to their children was found to inhibit the development of atopic eczema in the first seven years of life. Subsequent studies have failed to reproduce these results, however. The Committee therefore consid-

ers it premature to recommend the use of probiotics for the prevention of allergic disorders.

House dust mites and domestic pets. Mono-factor interventions involving the use of allergen-impermeable mattress and bedding covers have so far proved ineffective in the long-term primary prevention of asthma and allergy. Furthermore, there is no convincing evidence that non-allergic families should be advised not to keep pets in the interest of primary allergy prevention. Equally, there is no reason to believe that keeping a pet can reduce the likelihood of allergy.

Food allergens. The available clinical trial data do not suggest that a hypoallergenic maternal diet during pregnancy can prevent the initial development of atopic eczema in the first year of life. Not enough is yet known about the effectiveness of food allergen avoidance in infancy as a primary means of preventing allergic disorders to enable the Committee to make recommendations regarding such avoidance strategies.

Breastfeeding. Exclusive breastfeeding for at least the first three to four months of life reduces the likelihood of sensitisation, atopic eczema and asthma in the early years of life. However, some investigators have reported an increased longer-term risk of asthma and allergy following breastfeeding (albeit on the basis of studies in which the duration and exclusivity of breastfeeding was sometimes poorly defined). Although uncertainty exists concerning the duration of the beneficial effect on asthma and allergy, in view of the many other advantages of breastfeeding, the Committee would not recommend any change to the Netherlands Nutrition Centre's present advice, i.e. that infants should be exclusively breastfed for about six months.[490] This advice is consistent with that of the World Health Organization.[491]

Tobacco smoke. Although few good clinical trials have been performed to study the effect of limiting exposure to tobacco smoke on the development of asthma and allergy in young children, there are many sound reasons for preventing antenatal and neonatal exposure to tobacco smoke. This issue is considered in more detail in the Health Council's report on passive smoking.

Damp in the home. Various non-experimental studies have found evidence of a association between living in a damp home and the risk of asthma or allergy. However, it is not yet clear whether damp is primarily an indirect indicator of exposure to mite or fungal allergens or whether other factors in indoor air are responsible for the observed effects. The Committee does not therefore feel able to make practical recommendations at the present time regarding the avoidance of damp.

The Committee concludes that measures intended to influence individual environmental factors as a means of primary asthma and allergy prevention have so far proved relatively ineffective. However, the results of certain studies lead the Committee to be optimistic that bespoke multi-factor interventions may prove more effective. The best combinations of control measures for the various high-risk groups and the best time to implement such measures remain uncertain.

7.2 Recommendations to the government

There is convincing evidence that air pollution can be a negative influence on the progression of respiratory tract illnesses, including asthma. Action to reduce both indoor and outdoor air pollution is therefore desirable. Measures that might be considered in this context include the further discouragement of smoking, the reduction of traffic-related emissions and restrictions on the proximity of new housing and schools to busy traffic roads.

For the primary prevention of asthma and allergy, the Committee would like to see government policy focus on the following:

- stronger anti-smoking campaigns to make parents aware that smoking during pregnancy and early parenthood can influence the development of asthma and allergy
- promotion of other public information activities aimed at the prevention of asthma and allergy, particularly the encouragement of exclusive breastfeeding for at least three to four months (and, in view of the other benefits, possibly six months)
- encouragement of research into the effectiveness of multi-factor intervention It is not presently clear which combinations of control measures are effective and practicable, or which high-risk groups should be the targets of multi-factor intervention.

7.3 Recommendations regarding further research

7.3.1 Research into prevalence in the Netherlands

The absence of appropriate monitoring programs means that not enough is presently known about the prevalence of asthma and allergy in the Netherlands, or about changes in prevalence over time. Improved monitoring, starting with better monitoring of children, is therefore desirable. The Committee recommends involving the existing youth health care system. Children should be examined at

least once every five years to provide information about changes in prevalence over time. In this context, consideration should also be given to improving the identification of high-risk groups and risk factors.

The Committee recommends the adoption of a clear definition of and uniform diagnostic procedures for infant asthma, both within the health care system and in health research. The Local and National Monitor of Young People's Health operated by the Netherlands Association of Municipal Health Services, RIVM, TNO and ActiZ has great potential as a vehicle for the monitoring and early detection of asthma and allergy. The Committee would therefore like to see municipal health services adopting the recently developed and validated asthma and allergy question set. In addition to such questionnaire-based monitoring, the Committee recommends the periodic testing of small representative groups of subjects, so that changes in objective indicators, such as sensitisation, bronchial hyperresponsiveness and nitrogen monoxide exhalation, can be followed over time.

Finally, the Committee endorses the recommendation made by the Netherlands Association of General Practitioners, namely to adopt the international ARIA rhinitis classification system in the Netherlands, partly because it takes account of the effects of rhinitis on academic and occupational performance and on leisure activities.

7.3.2 Research into the roles of predisposition and environment

Uncertainty exists concerning various aspects of the role of environmental factors in asthma and allergy. These aspects include the following:

- the interaction between genes and environmental factors
- the possible beneficial effect of increased infection pressure on the development of allergic disorders
- the apparently contrasting effects of allergens and bacterial endotoxins
- the role of diet in the development of asthma and allergy
- the role of overweight in the development of asthma and allergy
- the influence of prematurity and low birth weight on the longer-term progression of asthma
- the role of outdoor air pollution in the development of asthma and allergy.

The Committee anticipates that the comprehensive analysis of data from studies currently in progress in the Netherlands and elsewhere will shed light on these matters.

7.3.3 *Research into preventive environmental control measures*

Not enough is presently known about the effectiveness of environmental control measures as a means of preventing asthma and allergy. Mono-factor interventions have not thus far proved very effective. The combination of control measures (multi-factor intervention) seems likely to be more effective, but much has yet to be learnt about which combinations are most effective, about when it is best to intervene, and about the practicability of intervention. Well-designed clinical trials of *mono*-factor interventions are costly, and the Committee recognises that trials of multi-factor interventions will be even more complex, making the scope for such trials somewhat limited. Another difficulty is that, where many control measures are concerned (such as stopping smoking or removing pets from the home), the blinding and randomisation of clinical trials are not possible. The Committee therefore recommends placing more emphasis on the evaluation of 'natural' experiments: there are many instances where people's everyday environments are changed for one reason or another, and much could be learnt by studying the effects of such changes. The Committee also recommends systematically analysing data from established studies into the natural course of asthma and allergy for evidence of the influence of environmental factors.

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A Request for advice

B The committee

C Organisations consulted within the community

D Glossary

Annexes

Annex **A**

Request for advice

On 18 February 2004, the State Secretary for Housing, Spatial Planning and Environmental Management wrote as follows to the President of the Health Council:

Report on asthma and respiratory allergy in relationship to environmental factors

Dear Mr. Knottnerus,

I am writing to ask the Health Council to provide me with a report on asthma and respiratory allergy in relationship to environmental factors.

Asthma and respiratory allergy are common disorders that have a major influence on quality of life. They are also substantial contributors to school and occupational absenteeism and to health care expenditure. Numerous publications have reported an increase in asthma and respiratory allergy, particularly among children, not only in the Netherlands but also in various other western countries. In Eastern and South-Eastern Europe, however, the prevalence of these disorders is much lower and has not exhibited the reported rise. A hereditary predisposition to allergic disorders (an atopic constitution) is believed to play an important role in the development of asthma and respiratory allergy. However, because changes in the genetic makeup of the population are gradual, it is believed that environmental factors, possibly in interaction with genetic factors, are primarily responsible for the reported increase in asthma and respiratory allergy, although it is not clear which factors are involved.

In the Netherlands and in other countries (particularly in Europe) numerous prospective studies have been started in recent years, with a view both to improving understanding of the development of asthma and other allergic disorders of the respiratory tract in children and to identifying influenceable factors. An evaluation of the results of these studies may be expected to shed light on the efficacy of preventive measures, such as allergen avoidance.

In view of the foregoing, I would like you to address the following questions:

1 Can the Health Council comment on the validity and significance of the data available concerning the prevalence of asthma and other allergic respiratory tract illnesses in the Netherlands and concerning the changes in the prevalence of these disorders in recent decades? Was the collection of the data in question sufficiently systematic that one may conclude that the prevalence of these disorders has actually risen over time?

2 Can the Health Council specify the nature and size of any population groups that are at particular risk of developing asthma or respiratory allergy, and indicate how suitable the present monitoring programmes are for tracking the prevalence of these disorders in the high-risk groups geographically and over time?

3 Can the Health Council indicate what is known about the contribution of and interactions between the various genetic and environmental factors that influence the initial development of asthma and respiratory allergy and the increasing prevalence of these disorders? Where are the main gaps in our understanding of these matters?

4 Finally, can the Health Council indicate what environmental control measures are likely to be most effective – for the various high-risk groups and in the various phases of life – both as means of preventing the initial development of asthma and other respiratory allergies and as means of improving the condition of asthma and respiratory allergy patients by reducing their complaints?

I should be grateful if the Health Council could provide me with a report concerning these matters by early 2005.

Yours faithfully,
P.L.B.A. van Geel
State Secretary for Housing, Spatial Planning and Environmental Management

Annex **B**

The Committee

The membership of the Committee that prepared this report was as follows:

- Prof. B. Brunekreef, *chairman*
  professor of environmental epidemiology, Institute for Risk Assessment Sciences, Utrecht University Medical Centre
- Prof. R.C. Aalberse
  professor of immunology, Sanquin, Amsterdam
- Dr. C.J.M. van den Bogaard, *adviser*
  medico-environmental inspector, VROM Inspectorate
- Prof. C.A.F.M. Bruijnzeel-Koomen
  professor of dermato-allergology, Utrecht University Medical Centre
- Prof. R. Gerth van Wijk
  professor of allergology, Erasmus Medical Centre, Rotterdam
- Prof. R.A. Hirasing
  professor of paediatric health care, VU Medical Centre, Amsterdam
- Prof. J.C. de Jongste
  professor of paediatric pulmonology, Erasmus Medical Centre, Rotterdam
- Dr. K.R. Krijgsheld, *adviser*
  senior policy adviser, Ministry of VROM
- Prof. J.G.R. de Monchy
  professor of allergology, Groningen University Hospital

- Dr. R. Pieters
  immuno-toxicologist, Institute for Risk Assessment Sciences, Utrecht University Medical Centre
- Prof. D.S. Postma
  professor of pulmonology, Groningen University Hospital
- Dr. A. Sachs
  Groningen GP, Julius Centre, Utrecht University Medical Centre
- Prof. C.P. van Schayck
  professor of preventive medicine, University of Maastricht
- Dr. H.A. Smit
  epidemiologist, National Institute of Public Health and the Environment, Bilthoven
- Dr. J.H. van Wijnen, *adviser* (since June 2006)
  doctor, epidemiologist, toxicologist
- M. Drijver, *secretary*
  Health Council, The Hague

For the preparation of this report, advice was also obtained from Dr M.M. Verberk, doctor, epidemiologist, toxicologist, Coronel Institute, University Medical Centre, University of Amsterdam.

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**

Organisations consulted within the community

The following bodies responded to the request to make suggestions on the subject of asthma, allergy and environmental factors:

- Dutch Asthma Foundation
- Association of Treatment Centres for the Chronically Ill
- National Hygiene and Safety Centre, Netherlands Association of Municipal Health Services
- National Working Group for Low-Allergen Homes
- Medical environmentalists at the municipal health services
- Health and Environment Reporting Network
- Dutch Association for the Critical Use of Vaccinations
- Dutch Association of Lung and Tuberculosis Doctors
- Netherlands Association for Paediatric Medicine
- Netherlands Association of General Practitioners.

Responses, suggestions and key publications were discussed in the Committee.

Annex **D**

Glossary*

Allergen

An agent that triggers an allergic immune response.

Allergic disorder

A disorder caused by an (IgE-mediated or other) allergic reaction, such as allergic rhinitis, allergic asthma, atopic eczema or food allergy.

Allergy or allergic reaction

A hypersensitivity reaction initiated by specific immunologic mechanisms.[25]

Antibody or immunoglobulin

Immunoglobulins (Ig) are proteins produced by the body, falling in one of the following five classes: IgG, IgA, IgM, IgD and IgE. Antibodies against a specific allergen, such as allergen-specific IgE, are produced by the body in response to exposure to that allergen.

Antigen

An agent that triggers an immune response. Such a response is desirable if the antigen is a pathogen that the immune system should resist. An antigen that triggers an allergic immune response is referred to as an allergen.

* Agreed with the Health Council's Food Allergy Committee, Allergen Standardisation Committee and Committee on Reform and Extension of the National Immunisation Programme.

Asthma

A chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells, eosinophils and T-lymphocytes. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. This inflammation also causes an associated increase in airway responsiveness to a variety of stimuli.[14,15]

Atopic march

If an individual develops a food allergy at a young age, it often proves to be one of the first of a series of atopic disorders. The phrase 'atopic march' is used to refer to the development of eczema, gastro-intestinal complaints and food allergy in the first five years of life, followed by rhinitis and allergic asthma later in life.[24,25]

Atopy

A personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms of asthma , rhinoconjunctivitis or eczema.[24,25]

Environmental factors

This report focuses on the physical environmental factors – as associated with chemical, physical and biological agents – that play a role in the initial development, control or aggravation of asthma and allergy.

Food allergy

A hypersensitivity reaction to a substance in food, involving the immune system.

Hypersensitivity

A state associated with objectively reproducible symptoms and phenomena caused by exposure to a precisely defined stimulus in dosages that most people can tolerate.

IgE

Type E immunoglobulin; see antibody.

Prevention

Preventing ill health in general or particular illnesses.[30]

primary prevention

Preventing new cases of an illness – in the broadest sense of the word – by removing its cause or causes[30]. In the context of this report, the

Committee has interpreted this as implying prevention of the first signs of asthma or allergy.

secondary prevention

The detection and treatment of illness before the 'patient' is aware of having it.[30] Where asthma or allergy is concerned, this might involve testing a person for bronchial hyperresponsiveness or sensitisation, before he or she has developed any asthmatic or allergic disorders.

tertiary prevention

Preventing the manifestation or aggravation of an illness that the patient already has[30]. In an asthma or allergy case, tertiary prevention might therefore mean controlling the manifestation of symptoms by, for example, avoiding contact with the stimuli or allergens that trigger attacks.

Probiotics

Living bacteria administered in food, which are capable of entering the intestines and thus exerting a beneficial effect.

Sensitisation

The demonstrable presence of allergen-specific antibodies or immunoglobulins (IgE) in the body. In the event of repeated exposure to the allergen, some sensitised people develop allergic symptoms.