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Effects of Indoor Air Pollution on Human Health
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Report No. 10
Effects of Indoor Air Pollution on Human Health

prepared by Working Group 4.

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- Report No. 1: Radon in indoor air.
- Report No. 2: Formaldehyde emissions from wood based materials: guideline for the establishment of steady state concentrations in test chambers.
- Report No. 3: Indoor pollution by NO₂ in European countries.
- Report No. 4: Sick building syndrome - a practical guide.
- Report No. 5: Project inventory.
- Report No. 6: Strategy for sampling chemical substances in indoor air.
- Report No. 7: Indoor air pollution by formaldehyde in European Countries.
- Report No. 8: Guideline for the characterization of volatile organic compounds emitted from indoor materials and products using small test chambers.
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SUMMARY

This report contains a summary discussion of human health effects linked to IAP in homes and other non-industrial environments. Rather than discussing the health effects of the many different pollutants which can be found in indoor air, the approach has been to group broad categories of adverse health effects in separate chapters, and describe the relevant indoor exposures which may give rise to these health effects.

The following groups of effects have been considered: effects on the respiratory system; allergy and other effects on the immune system; cancer and effects on reproduction; effects on the skin and mucous membranes in the eyes, nose and throat; sensory effects and other effects on the nervous system; effects on the cardiovascular system; systemic effects on the liver, kidney and gastro-intestinal system. For each of these groups, effects associated with indoor air pollution (IAP), the principle agents and sources, evidence linking IAP to the effect(s), susceptible groups, the public health relevance, methods for assessment, and major research needs are briefly discussed.

For some groups of effects, clear relationships with exposure to IAP have been reported in the world literature. Among these are respiratory disease (particularly among children), allergy (particularly to house dust mites) and mucous membrane irritation (particularly due to formaldehyde). Large numbers of people have been, and are still being affected.

Many chemicals encountered in indoor air are known or suspected to cause sensory irritation or stimulation. These, in turn, may give rise to a sense of discomfort and other symptoms commonly reported in so-called “sick” buildings. Complex mixtures of organic chemicals in indoor air also have the potential to invoke subtle effects on the central and peripheral nervous system, leading to changes in behavior and performance.

An increased risk of developing lung cancer has been linked to exposure to environmental tobacco smoke (ETS) and to radon decay products. Lung cancer is a very serious disease with a high fatality rate; however, the number of people affected is much lower than the number of people contracting respiratory disease or allergies, or experiencing irritative effects due to exposure to indoor pollution.

The effects of IAP on reproduction, cardiovascular disease and on other systems and organs have not been well documented to date. To a certain extent, this may mean that no serious effects occur, but there has been little by way of research to clearly document the absence of these types of effects.
1. PREFACE

The impact of IAP on man may consist of undesired health effects of different types, ranging from sensory annoyance or discomfort to severe health injuries. "Health" is defined, for the purpose of this report, according to the well-known WHO definition as "A state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity". The public health relevance of the effects of IAP varies, not only from substance to substance, but also from country to country, depending on the presence of specific local sources and climatic influences.

Specific investigations of these effects have only recently been undertaken, but in some cases epidemiological evidence of their occurrence has already been obtained. For other effects, data supporting their likely occurrence derive from related disciplines and are mainly based on experimental studies or models for assessment and prediction of risk.

This document briefly describes the health effects of IAP with the objective of providing a basic core of information accessible to experts belonging to different disciplines.

Besides the identification of the health effects which are or may be caused by indoor pollutants, this report describes the methods available for the study of the effects concerned.

The health effects are presented by organ or system affected and by type of effect. It should be noted that several of these effects may be present simultaneously or may be caused by the same agents or sources. Each effect is described using the same format:

- definition of the effect
- indoor agents that may cause it
- evidence linking the effect to IAP
- susceptible groups in the population
- relevance for public health
- methods available for the assessment of this effect
- major research needs.

The information given in this report has been derived from a series of scientific documents and publications that have resulted from the deliberations of international groups of experts such as the Working Groups on Indoor Air Quality of the WHO Regional Office for Europe in Copenhagen, the Concertation Committee of the European Concerted Action on Indoor Air Quality and its Impact on Man (formerly COST project 613), and the International Conferences on Indoor Air Quality and Climate. Also consulted were recent comprehensive reviews of the topic. A selected list of references is given at the end of the report.
2. GENERAL ASPECTS OF ASSESSMENT OF HUMAN HEALTH EFFECTS OF IAP

2.1. Assessment of human exposure to IAP

Human exposure to indoor air pollutants is difficult to quantify due to the fact that it is largely determined by micro-environmental characteristics. Pollution levels in one home may be quite different from those in another, depending on the presence and usage of sources of pollutants and on the ventilation habits. Also, many techniques routinely used for measuring ambient air pollution are not suitable for indoor surveys because of cost, bulk, noise or amount of air displaced. A range of miniaturised measuring devices has been developed for indoor use. However, most of these techniques measure average concentrations over several hours or even days, which limits their use in studies of pollutants with acute effects such as carbon monoxide (CO) or with effects believed to be related more to short term peak levels than long term averages, such as nitrogen dioxide (NO₂). Other pollutants such as environmental tobacco smoke (ETS) and some volatile organic compounds (VOC) are of interest for their suspected chronic effects related to long term exposure. For pollutants such as these, measurement techniques which average concentrations over extended periods are sufficiently informative. For some substances, techniques have been developed for personal monitoring as well, which require subjects to carry the equipment with them wherever they go. In practice, this has proved to be most feasible for substances that can be measured with so-called "passive" monitors which rely on diffusion of pollutants to an absorbing surface without the need of pumps and associated equipment.

If measurement of exposure is not feasible, a modelling approach is sometimes useful. Existing models for estimating human exposure make use of data on time usage patterns, source presence, strength and use, and other relevant data. They need to be validated in studies in which exposure is actually measured. The advantage of modelling rather than measuring exposure is that modelling can usually be done at a fraction of the cost.

For some pollutants, biological monitoring offers a viable alternative to either measuring or modelling exposure in air. In biological monitoring, substances (or their metabolites) are measured in, for example, exhaled air, blood or urine. If the relationship between the levels in biological media and environmental levels are adequately characterised, biological monitoring offers a unique picture of integrated exposure of humans to pollutants.

2.2. Increased human susceptibility to pollutants

The human race is extremely diverse, and it is no wonder that there are differences in susceptibility to pollutants between equally exposed individuals. Variations in susceptibility may range from gradual differences to the very dramatic differences shown, for example, by persons sensitised to certain allergens. When there are no specific mechanisms or factors underlying differences in susceptibility variations in susceptibility are believed to follow a roughly normal distribution. Many specific mechanisms or factors have, however, been shown or suggested to be associated with sometimes large differences in susceptibility. Among these are genetic
factors, age, gender, nutritional status, pre-existing disease, allergy and asthma, and tobacco smoking.

a. Several genetic factors have been shown to be associated with the development of chronic obstructive pulmonary disease (COPD). The enzyme alpha-1-antiprotease, for example, inhibits proteolytic enzymes; deficiency of this enzyme is heritable, and the incidence of emphysema has been shown to be much greater in patients who are homozygous for this particular deficiency.

b. Marked differences in mortality due to ozone exposure have been shown to exist between dogs and some rodent species, presumably due to a more efficient removal of ozone in the upper respiratory system of the dogs.

c. Young children, infants and the foetus are known to be more susceptible to adverse effects of lead at a given blood lead level than adults.

d. Diets deficient in selenium or vitamin E have been shown to increase lung damage due to ozone exposure in laboratory animals.

e. Asthmatics are known to be more susceptible to given concentrations of sulphur dioxide ($SO_2$) and nitrogen dioxide ($NO_2$) than non-asthmatics.

f. Smoking and asbestos exposure have been shown to act synergistically in the causation of lung cancer; smokers suffer from COPD more than non-smokers, and to the extent that COPD patients are more susceptible to pollutants than others, smoking causes some people to be more susceptible. It is not clear to what extent smokers who do not have COPD are more susceptible to effects of other pollutants than non-smokers.

These are but a few examples of differences in susceptibility to pollutants which may exist between humans with different characteristics. In the separate chapters, specific examples will be given of groups thought to exhibit increased susceptibility to the health effect under consideration.

2.3. Methods of studying health effects

Methods of studying health effects of indoor pollutants can be grouped into three broad categories:

a. Human studies, subdivided into observational and experimental studies. Epidemiological studies of pollutants are mostly observational, i.e. the investigator has no means of experimentally exposing humans to pollutants, or of allocating subjects to exposed and unexposed groups. Critical issues are therefore the validity and precision of exposure assessment, and the control for confounding factors in these studies. Recent developments have stressed the importance of reducing exposure misclassification, and of studying restricted, well defined, homogenous populations to address these issues. The main advantage is that humans are studied under realistic
conditions of exposure. By themselves, observational epidemiological studies are not usually sufficient to support causality of an observed association, so that additional information is needed from other types of studies. Experimental studies are among these; however, these are only suitable for studying moderate, reversible, short term effects in persons who are healthy or only moderately ill. Their main advantage is that exposure conditions and subject selection are under the control of the investigator.

b. Animal studies, which can be subdivided into a number of categories depending on their length (acute, subchronic, chronic) or end-point (morbidity, mortality, carcinogenicity, irritation, etc.). Here, the investigator has full control over exposure conditions and health effects studied. However, the principle limitations lie in the fact that extrapolation from the studied animal species to man is always necessary. Also, while in human populations health effects with low incidences are often of interest (e.g., specific cancers), it is not feasible to study very large groups of animals to detect these low incidences. In practice, therefore, animal experiments are often carried out using very high experimental doses to compensate for the relatively small number of animals used and as a consequence, an additional extrapolation from high to low doses is also often necessary.

c. In vitro studies, in which effects of pollutants on cell or organ cultures are studied. These studies have the advantage that they are less costly than animal studies, and that results can generally be obtained in a shorter period of time. They are useful for studying mechanisms of action, but it is not usually possible to predict effects on whole organisms from their results in a quantitative way.

In the following chapters, additional remarks will be made on specific methods used to study the health effects under consideration.

2.4. Criteria for the assessment of the impact of IAP on the community

The process of risk characterisation for indoor pollutants occurs through several phases: hazard identification, exposure assessment, dose-effect evaluation, and finally qualitative and quantitative risk assessment. The final product of this process may be an individual risk estimate per exposure unit or the evaluation of the incidence of the concerned effects in a given population.

The risk characterisation through a multi-stage process as described above is particularly informative because, by dividing the analysis of the scenario of each pollutant into steps, it allows the separate recognition of the importance of each variable in the scenario and the prediction of the changes of frequency or severity of effects obtainable by modifying (increasing or decreasing) exposure.

For some types of IAP, our understanding of human health risk is well defined. For most indoor air pollutants, however, the risk assessment process has its limitations. First, it has been applied successfully only to individual pollutants for which information is available for exposure and dose-response relationships and for which the effect is
clear, certain, and measurable, such as mortality and cancer. Little progress has been made in applying the risk assessment process to environmental issues involving pollutant mixtures or effects for which the causes are difficult to ascertain precisely, such as in heart disease, allergic reactions, headache, and malaise. A different approach is needed for the assessment and characterization of the risks associated with most indoor air pollutants.

A basic and simple criterion for assessing the importance of the health risk related to indoor pollution makes reference to the severity of the effect concerned and to the size of the population affected. The resulting 2 x 2 matrix is shown in Table 1. Important issues for the community may come from severe health impacts, particularly when affecting a large segment of the population. Minor impacts, such as those related to discomfort or annoyance may, however, become important when a large number of individuals in the community are concerned.

Table 1. General matrix for the evaluation of the impact of indoor pollutants on the community.

<table>
<thead>
<tr>
<th>Health impact</th>
<th>Severe effects</th>
<th>Minor effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of people affected</td>
<td>death</td>
<td>mild disease</td>
</tr>
<tr>
<td></td>
<td>cancer</td>
<td>discomfort</td>
</tr>
<tr>
<td></td>
<td>serious disease</td>
<td>annoyance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>reduced productivity</td>
</tr>
<tr>
<td>&gt;10% of the population</td>
<td>large exposure - large health impact</td>
<td>large exposure - limited health impact</td>
</tr>
<tr>
<td>&lt;10% of the population</td>
<td>limited exposure - large health impact</td>
<td>limited exposure - limited health impact</td>
</tr>
</tbody>
</table>

2.5. The "Sick Building Syndrome"

Since the early 1970s, numerous outbreaks of work related health problems have been described among employees in buildings or offices not directly contaminated by industrial processes. Two broad categories can be distinguished: those characterised by a generally uniform clinical picture for which a specific cause has been identified, and those in which affected workers reported nonspecific symptoms occurring only during the time when they were at work.

The former episodes have been defined "Building - Related Illness" (BRI), the latter, "Sick Building Syndrome" (SBS). Symptoms reported in SBS have typically included mucous membrane and eye irritation, cough, chest tightness, fatigue, headache and malaise.
In outbreaks of BRI, a wide spectrum of causative factors has been implicated: immunologic sensitizing agents, infectious agents, specific air contaminants, and environmental conditions, such as temperature and humidity. Outbreaks without an identifiable cause have frequently occurred in new, sealed office buildings and have for that reason also been called the "tight building syndrome" (TBS).

Essential for SBS are the concepts of comfort, well-being and air quality. Comfort or well-being refers to a status of optimal physical conditions for the body. Acceptable indoor air quality is described as air in which there are no known contaminants at harmful concentrations and with which a substantial majority (e.g., 80% or more) of the people exposed do not express dissatisfaction.

Thus, the "Sick Building Syndrome" is a term used to describe the reduced comfort and health status of occupants in a particular building or part of it where the occupants complain about indoor air quality and manifest symptoms which they assign to that reduced quality.

A recent definition by WHO defines SBS as a reaction to the indoor environment among a majority of the occupants whose reactions can not be related to obvious causes such as excessive exposure to a known contaminant or a defective ventilation system. The syndrome is assumed to be caused by a multifactorial interaction of several exposure factors involving different reaction mechanisms.

The symptoms of SBS are mainly reports of discomfort or the feeling of being "less than well". Most of the symptoms are not usually accompanied by independently observable signs, so that self-reports are the only means by which incidence and prevalence can be determined.

The criteria for the definition of SBS are summarised in Table 2. More details on the SBS can be found in a monograph prepared by a group of experts for the Committee of the COST 613, and the reader is referred to that document for further information (see References).
Table 2. Criteria for the definition of the Sick Building Syndrome

A high proportion of the occupants of the building must be reacting. Symptoms and reactions observed belong to the following groups:

A. Acute physiological or sensory reactions
   - Sensory irritation of mucous membranes or skin
   - General malaise, headache and reduced performance
   - Unspecific hypersensitivity reactions, dryness of skin
   - Odour or taste complaints

B. Psychosocial reactions
   - Decreased productivity, absenteeism
   - In contact with primary health care
   - Initiatives to modify the indoor environment

Sensory irritation in eyes, nose and throat must be dominating.
Systemic symptoms (e.g. from stomach) must be infrequent.
No obvious causality can be identified in relation to high exposure to single agents.
3. EFFECTS OF IAP ON THE RESPIRATORY SYSTEM

As the human respiratory system is the organ directly affected by air pollution, the potential respiratory health effects of indoor and outdoor air pollution have been widely investigated. This section is restricted to non-carcinogenic and non-allergic effects on the lower airways (below the larynx). Allergic effects are considered in chapter 4; carcinogenic effects are treated in chapter 5; upper respiratory effects are treated in chapter 6.

3.1. Respiratory health effects associated with exposure to IAP

Several effects on the respiratory system have been associated with exposure to IAP. These include acute and chronic changes in pulmonary function, increased incidence and prevalence of respiratory symptoms, acute in pre-existing respiratory symptoms, and sensitisation of the airways to allergens present in the indoor environment. Also, respiratory infections may spread in indoor environments when specific sources of infectious agents are present, or simply because the smaller indoor mixing volumes allow infectious diseases to spread more easily from one person to the next. The latter mechanism is particularly operative in schools, nursery schools, etc.

Observed changes in pulmonary function due to exposure to, e.g., tobacco smoke in the home, have mostly been due to acute or chronic airway narrowing leading to obstruction of air flow. This is measured as a reduction in the quantity of air that can be exhaled in one second after deep inspiration (FEV1), and a limitation in the various measures of air flow such as Peak Expiratory Flow (PEF), Maximum Mid Expiratory Flow (MMEF), and Maximum Expiratory Flow at x% of Forced Vital Capacity (MEFx). In growing children, it has also been suggested that lung development could be impaired by exposure to IAP.

Asthma, manifested by attacks of excessive airway narrowing leading to shortness of breath and wheezing, can be caused or aggravated by exposure to allergens in the home, but it has also been associated with exposure to substances such as nitrogen dioxide and environmental tobacco smoke (ETS). Bronchitis, manifested in inflammatory changes in the airways and mucus hypersecretion has been linked to high levels of ambient air pollution in the past, and to exposure to ETS in the home in recent studies. Respiratory symptoms which have been associated with exposure to indoor air pollutants are symptoms mostly related to the lower airways such as cough, wheeze, shortness of breath and phlegm. The distinction between acute and chronic changes in respiratory symptoms is not always clear; this is partly a matter of the methods used to investigate them (see below).

In contrast to the occurrence of chemical pollutants in indoor air, attention to which has grown considerably over the past two decades, the role of infectious agents in indoor air has been known for a long time. Infectious agents can be involved in the inflammatory conditions rhinitis, sinusitis, conjunctivitis and sinusitis, in pneumonia, in asthma and in alveolitis.
3.2. Principle agents and sources

Combustion products, ETS and biological contaminants are the main agents associated with respiratory health effects indoors. Of the combustion products, nitrogen dioxide (NO$_2$) has been widely investigated, but it has not been unequivocally shown that it is actually causing respiratory health effects in the concentration range in which it is normally encountered indoors. NO$_2$ concentrations are elevated in homes where unvented gas appliances are used. Peak concentrations of up to several thousand IJg/m$^3$, which is well above the 1987 WHO health guidelines, are known to occur relatively frequently in homes. Non-intended usage of unvented gas appliances (heating, cloth drying) may increase concentration levels for extended periods of time. In homes where unvented kerosine heaters are in use, elevated levels of sulphur dioxide (SO$_2$) may also occur, when sulphur containing fuels are used. Especially in climate zones with temperate winters, where homes may not be equipped with permanent heating systems, unvented kerosine heaters may be a significant source of indoor pollution.

In industrialised countries, ETS is probably the most important indoor cause of non-carcinogenic adverse effects on the respiratory system. It has been shown that long term average concentrations of suspended particulate matter in indoor air are significantly higher in smokers' homes than in homes where the inhabitants do not smoke. In contrast, levels of carbon monoxide (CO) and NO$_2$ are not markedly increased in smokers' homes, indicating that for these substances, other sources are predominant. Effects of ETS on respiratory symptoms and pulmonary function of children have been observed by many investigators. Effects on adults have been demonstrated less unequivocally.

Contaminated humidifiers or humidification sections of HVAC (Heating, Ventilating and Air Conditioning) installations are often sources of infectious agents (such as Legionella pn.). Infectious agents may also proliferate in other locations which, generally speaking, meet their needs in terms of substrate, temperature and humidity. HVAC installations are found to contain and spread biological contaminants relatively frequently, due to poor design, operation and/or maintenance. In homes, sources of biological contaminants are more often formed by damp areas on walls and floors. This is dealt with further in chapter 4.

3.3. Evidence linking IAP to non-carcinogenic effects on the respiratory system

The evidence that links indoor exposure to combustion products, ETS and biological agents to non-carcinogenic effects on the respiratory system stems to a large extent from epidemiological studies.

Of the combustion products, NO$_2$ has been studied widely in the past decade. Many studies have used proxy measures of exposure rather than actual NO$_2$ measurements by contrasting populations living in homes with unvented gas cooking appliances with populations living in homes equipped with electric cookers. It has been shown that this may lead to a sizable misclassification of exposure to NO$_2$. Some studies have used indoor and personal monitoring of NO$_2$ instead, usually by employing diffusion samplers which require exposure times of several days to a week.
As a result, only long term average exposure levels were available in these studies. Animal experiments have suggested that repeated exposure to peak concentrations may be more harmful to health than exposure to long term average concentration levels resulting in the same inhaled dose. As peak concentration levels do occur in homes, and as their relationship with long term average concentration levels is likely to be weak, exposure to NO₂ may have been inadequately characterised even in those studies that have employed large scale passive sampling of NO₂ in homes and on persons. It is conceivable that the inconsistency of the results of epidemiological studies conducted so far is partly related to this issue, as peak concentration levels in homes have been shown to exceed the 1987 WHO health guidelines by a fairly large margin in a fairly large proportion of homes.

Exposure to ETS has been shown by many investigators to be related to lower respiratory illness in infancy, and to the development of chronic respiratory symptoms in older children. In addition, pulmonary function in exposed children is reduced compared to pulmonary function in unexposed children. To some extent, this may be a carry over from effects on the foetal lungs caused by smoking in pregnancy, but there is also some evidence which suggests that development of lung function of exposed children is actually lower than that of unexposed children. Among adults, evidence for non-carcinogenic effects of exposure to ETS has been less unequivocal. However, there are some studies which suggest that non-smoking women who have been married to a smoker for a long time, do have a reduced lung function compared to unexposed women.

Several infectious diseases are known to be transmitted from one person to the next when infectious agents are propelled into the air by coughing, sneezing, singing, talking, etc. The major reason why airborne infections are much more likely to spread indoors than outdoors is, that the dilution in outdoor air is usually so great that chances of inhaling enough infectious droplet nuclei to become infected are negligible. Also, people spend much more time indoors than outdoors, especially in winter when respiratory infections are generally more prevalent than in summer. Several studies have linked "Legionnaires disease", humidifier fever and bronchopulmonary aspergillosis to agents spread by contaminated HVAC systems or resulting from refurbishing of hospitals. There is little evidence that biological contamination of homes can lead to these specific diseases, although isolated cases have been known to occur.

Evidence for effects of other biologic contaminants on the respiratory system is discussed in chapter 4.

3.4. Susceptible groups

The respiratory system of young children is considered to be more susceptible to environmental insults than that of adults. Also, children have faster respiratory and metabolic rates compared to adults. Elderly people with impaired pulmonary function and/or weakened defence systems may also be more at risk, as an insult of a given size will affect them more than people with a larger reserve capacity. Smoking may also increase susceptibility to indoor air pollutants. In addition, patients already
suffering from Chronic Obstructive Pulmonary Disease (COPD) are considered to be more susceptible than healthy individuals.

Once sensitised, people suffering from allergies are orders of magnitude more sensitive to allergens and to some other pollutants than the non-sensitised population. A special population at risk are unborn children whose mothers smoke, as they are exposed to noxious substances in utero. Another susceptible group is people exhibiting an increased degree of nonspecific bronchial reactivity and/or asthma.

Another group susceptible to contracting respiratory infections are those with any impaired ability to fight off infections including persons with immunodepressive conditions as associated with, for instance, AIDS and cancer; young children; the elderly; persons with existing disease such as chronic obstructive lung disease; and possibly those who may be more susceptible to infections due to exposure to irritating agents such as NO₂ which may damage mucociliary cells etc.

3.5. Public health relevance

A large segment of the population is exposed to ETS, to combustion products from unvented combustion appliances, and to biological contaminants in the home. The smoking habit is still so prevalent in many European countries that smokers are present in over 50% of the households. Effects of exposure to ETS on the respiratory system of children are well documented, and sizeable public health benefits can be achieved when smoking in private homes is discouraged. Respiratory disease is relatively common among children, and even if a reduction in exposure to ETS would result in a 10% decrease in incidence, a very large number of respiratory disease episodes would be prevented. Even if relative risks are small, as seems to be the case with risks associated with exposure to NO₂ in the home, attributable risks may be of some concern when many are exposed. Dampness in homes is a reviving area of concern, partly due to building practices which, in reducing ventilation, may cause moisture to be trapped inside new homes. Home dampness may enhance growth of mites and fungi, which produce substances that may sensitise susceptible individuals.

The public health relevance of infectious diseases caused by indoor contamination is not easy to assess. It has been noted that a substantial proportion of disease and absenteeism from work or school is associated with infectious episodes caused by indoor air exposure to infectious agents. To the extent that such exposure is preventable by reducing proliferation of infectious agents in buildings or by immunisation, air irradiation or minimisation of crowding, the public health relevance of indoor factors leading to infectious diseases could be sizable.

3.6. Methods for assessment of non-carcinogenic effects on the respiratory system

For the investigation of respiratory health effects, human epidemiological and experimental studies, animal and other laboratory experiments (see chapter 2.3) can be employed.

Epidemiological studies have been widely used, mostly focussing on pulmonary function and respiratory symptoms. A fairly high level of standardisation has been
reached in this field. In the U.S., an extensive set of guide-lines on pulmonary function testing as well as the use of respiratory symptom questionnaires was published by the American Thoracic Society (ATS) in 1978. In 1987, the guidelines for pulmonary function testing were updated. In Europe, the European Community for Coal and Steel (ECCS) published guidelines for pulmonary function testing in 1983. For the assessment of respiratory symptoms, the questionnaire of the British Medical Research Council (BMRC) has been used for decades to investigate symptoms in adults. Questionnaires for children have been developed by the ATS, WHO and EC. The WHO and EC questionnaires have both been used in international collaborative studies in the 70s. Despite the existence of these questionnaires, many investigators use their own or include modifications. Validation of these questionnaires has been incomplete.

Less frequently applied in epidemiological studies are measurements of hypersensitivity and non-specific hyperreactivity. Histamine, methacholine and cold air have been used to provoke bronchoconstriction in such studies; sometimes, bronchodilators have been used instead of bronchoconstrictive agents. To study hypersensitivity, specific extracts of allergens have been used in skin tests and in bronchial provocation tests. Also, measurement of antibodies in serum has been performed. Short term changes in respiratory symptoms can be studied by using symptom diaries, in which day-to-day changes in symptoms are recorded by or for study subjects. The advantage of epidemiological studies is that human populations are studied under normal living conditions, which makes their findings highly relevant from a public health point of view. The major disadvantage is that it is difficult to control for other potential determinants of the health effect which is being studied.

Human experimental studies have been used to study short term, reversible changes in pulmonary function and respiratory symptoms in volunteers. The methods to study effects can be more sophisticated than in epidemiological studies. Exposure conditions are under control of the investigator. The major disadvantage is that only short term, reversible changes can be studied.

Small, airway disfunction as measured by pulmonary function tests (MEF25, N2 washout curves) has been suggested as a marker for early damage to the lung; tests of non specific bronchial hyperreactivity have been suggested as a means to identify a susceptible sub population; skin tests can be used to identify sensitised individuals.

As the agents responsible for infectious disease are of biological origin, the methods to measure effects do not only include confirmation of signs and symptoms, but also isolation, culture and identification of the micro-organisms involved.

### 3.7. Major research needs

The health effects of IAP have recently been reviewed by Samet et al. (1987, 1988). These authors identified research needs for exposure to ETS: mechanisms of injury have not been adequately identified, and the relative importance of exposures 'in utero', in infancy, and later in childhood has not been examined; for adults, there is no consensus on effects of ETS on pulmonary function and respiratory symptoms. For
NO$_2$, groups with particularly high exposures (e.g., people who use their cooking stove for heating and clothes drying) have not been adequately studied. Future studies should also make more use of direct measurements of exposure. In terms of mechanisms, the relationship between non-specific and specific airway reactivity needs further elucidation.

There is a need to further improve building and HVAC system design in such a way that chances for proliferation of potentially hazardous micro-organisms are minimised. The role of infectious disease in SBS needs to be further elucidated. Also, the extent to which infections are responsible for increased prevalences of symptoms in damp homes requires further investigation.
4. ALLERGY AND OTHER EFFECTS OF IAP ON THE IMMUNE SYSTEM

The immune system is characterised by the ability to recognise and react specifically with foreign macromolecular material. This ability is mostly beneficial and plays an important part in resistance to infectious disease, but sometimes results in adverse effects such as allergic or hypersensitivity diseases of the respiratory system.

Indoor as well as outdoor air pollutants may induce an immunological sensitisation in susceptible individuals in whom any future contact with the pollutant (the allergen) may elicit an outbreak of disease.

This section is restricted to the description of allergic effects in the respiratory system.

4.1. Allergic diseases associated with exposure to IAP

Allergic asthma and extrinsic allergic alveolitis (hypersensitivity pneumonitis) are the two most serious allergic diseases caused by allergens in indoor air. Allergic rhinoconjunctivitis and humidifier fever are other important diseases; it is not clear if or how the immunological system is involved in humidifier fever.

Allergic asthma is characterised by reversible narrowing of the lower airways. Pulmonary function during an attack shows an obstructive pattern in serious cases together with reduced ventilation capacity. Allergic asthma may be caused by exposure to indoor air pollutants, either acting as allergens or as irritants. Immunological specific IgE sensitisation to an airborne allergen is a major component of this disease, but non-specific hypersensitivity is also important for the asthmatic attacks occurring on exposure to irritants in the indoor air.

The prevalence of asthma varies considerably from country to country. Although asthmatic attacks seldom lead to death, the costs of medical care are considerable in terms of hospital admissions, medication, and lost work days.

Allergic rhinoconjunctivitis is also an IgE-mediated disease, but while asthma occurs in all age groups, allergic rhinoconjunctivitis is especially prevalent among children and young adults. The main symptoms are itching of the eye and/or the nose, sneezing, watery nasal secretion and some stuffiness of the nose. The severity of the symptoms varies with the exposure to the allergen. Individuals often suffer from both allergic asthma and allergic rhinoconjunctivitis and are seldom sensitive to only one allergen. Aeroallergens from house dust mites, pets, insects, moulds, and fungi in the indoor air have been shown to be associated with allergic asthma and/or rhinoconjunctivitis.

Extrinsic allergic alveolitis, also called hypersensitivity pneumonitis, is characterised by recurrent bouts of pneumonitis or milder attacks of breathlessness and flu-like symptoms. Studies of the pulmonary function during an acute episode will usually show a restrictive pattern with a decreased diffusion capacity. The disease is believed to be an inflammatory reaction in the alveoli and bronchioles involving circulating antibodies and a cell-mediated immunological response to an allergen. For
example it occurs in farmers as a result of handling mouldy hay ("farmer’s lung") and in pigeon breeders due to bird droppings. However, the disease has also in a few cases been associated with exposure to IAP, most frequently related to humidifiers in homes and offices contaminated with bacteria, fungi, or protozoans.

Allergic asthma and extrinsic allergic alveolitis resolve with cessation of exposure to the allergen, but continued exposure in sensitised patients may result in permanent lung damage and death from pulmonary insufficiency.

Humidifier fever is a flu-like illness involving the immune system, in which X-ray abnormalities are usually absent. The exact cause is not clear. The disease may occur among persons exposed to humidification systems contaminated with microbial growth. The symptoms typically occur 4-8 h after the exposure on the first day back at work after a weekend, but resolve within 24h. Despite continuous exposure the disease does not recur until after the next weekend. Even though pulmonary changes are seen during attacks of humidifier fever, the disease does not lead to permanent lung damage.

4.2. Principle agents and sources

House dust mites, pets, insects, and moulds in the indoor environment are important causes of allergic asthma and rhinoconjunctivitis. Outdoor allergens such as pollens and moulds may penetrate into the indoor environment through open windows, doors, or ventilation systems. The airborne allergens vary with seasons, weather conditions, geographical location, and the local indoor environment.

House dust mites, Dermatophagoides pteronyssinus and D. farinae, are prevalent in climates where winters are humid and mild, but they can also live elsewhere as long as a microenvironment with a high humidity (>45%) and temperatures between 17°C and 25°C is provided. House dust mites and their debris and excrements, that contain the allergens, are normally found in the home in beds, mattresses, pillows, carpets and furniture stuffing, but they have also been found in office environments. The dust mite allergens may become airborne during indoor activity.

Domestic animals such as cats, dogs, birds, rodents and horses may cause allergic asthma and rhinoconjunctivitis. Allergens are found in different amounts in dandruff, hair, saliva, and urine from the animals. The exposure usually occurs in homes, but also in schools and kindergartens where domestic animals are kept as pets or for education. Close contact with people keeping animals may also give rise to allergic reactions. Shed skin scales, dried secretions, and faecal particles from insects may also cause allergic asthma and rhinoconjunctivitis. Cockroaches are an important source of allergens in homes with poor sanitary conditions.

Moulds require a high humidity (>70%) to grow. There is a large variety of moulds and many of them have very specific growth requirements. Mould allergens are mostly found outdoors in living mould organisms, spores, and particles even smaller than spores. However, they may penetrate into the indoor environment such as pollens. Persistent damp areas, ie, bathrooms and basements, may support abundant mould growths indoors, but also water seepage in building material causing damp ceilings.
walls, carpeting, and furniture may provide favourable conditions of growth for moulds. Furthermore, draught-proofed ("tight") buildings may offer ideal places for mould growths when the indoor humidity is high and moisture condensation on cold areas on walls and windows occur.

Contaminated humidifiers in homes, industrial and non-industrial buildings and cars have been associated with allergic asthma, humidifier fever, and extrinsic allergic alveolitis. The contaminated humidifiers generate aerosols loaded with microorganisms and debris of microorganisms, and a wide range of microorganisms, including thermophilic actinomycetes, moulds, bacteria, amoebae, and nematodes, have been described as sources of offending allergens.

4.3. Evidence linking IAP to allergic effects

Most of the evidence that links IAP to allergic effects comes from individual case reports and small series of outbreaks which resulted in comprehensive clinical descriptions.

The diagnosis of the allergic disease is based on the clinical history and signs, evidence of exposure, the presence of specific antibodies, response to inhalation challenge, and improvement with cessation of exposure.

In many cases the major allergens for allergic asthma or rhinoconjunctivitis have been identified, while identification of the causative allergens for extrinsic allergic alveolitis has often been uncertain. For humidifier fever it is debatable whether the disease is caused by exposure to allergens, bacterial endotoxins or other toxins, but it is known that the cause lies in the biological contamination of the humidifiers.

Epidemiological studies have shown that exposure to mites in homes during childhood is a major risk factor for the development of allergic asthma. Reports suggest that for mite allergy a level of 100-500 mites/g house dust should be regarded as a maximum acceptable contamination. Otherwise there is for non-industrial indoor air allergens, no knowledge of the dose response relationships apart from the fact that allergy to animals is very unlikely to develop when not exposed daily at home or at work.

4.4. Susceptible groups

All human beings have IgE antibodies and can make specific IgE antibodies against a number of allergens. A minor part (10-12%) of the population respond easily to allergen exposure by making specific IgE antibodies and developing allergic asthma and/or rhinoconjunctivitis. This ability is genetically determined although not in a simple way. Outdoor air pollution, ETS, and certain types of infections possibly play a contributive part in the allergic breakthrough. There are no cases of extrinsic allergic alveolitis being hereditary, but non-smokers seem more susceptible to the disease.
4.5. Public health relevance

The medical expenses associated with allergic diseases are considerable. The prevalence and incidence of allergic disease due to IAP have not been studied. However, the overall prevalence of allergic asthma and rhinoconjunctivitis may be as high as 20%, and a major proportion of the patients suffering from asthma who are referred to a clinic are allergic to house dust mites and pets. A high prevalence of allergy to mould has also been reported in some series of patients with allergic asthma. Establishing the diagnosis of allergy to a certain allergen requires standardised allergen preparations which are lacking for most allergens and therefore make the estimation of the relative importance of the different allergen exposures difficult. Extrinsic allergic alveolitis and humidifier fever are rare diseases in the indoor environment, but epidemics in office buildings have been seen.

One of the major concerns is what happens when buildings are made more energy-efficient by reducing ventilation and increasing insulation. This may lead to condensation of water from cooking, showering, etc and therefore higher indoor humidity, creating a favorable environment for house dust mites and moulds.

As the major causes of allergic asthma seem to be house dust mites, pets, and in some areas, cockroaches, this disease is highly preventable by appropriate building design and building use. Likewise, proper maintenance of humidifiers will reduce the occurrence of extrinsic allergic alveolitis and humidifier fever in the indoor environment.

4.6. Methods for assessment of allergic effects of IAP

Even though the usual investigation methods are applicable for assessing the allergic effects of IAP (see chapter 2.3), in the main clinical studies have been made. As already mentioned, the diagnosis of the allergic disease is based on the clinical history and signs, evidence of exposure, the presence of specific antibodies, response to inhalation challenge, and improvement with cessation of exposure, and a thorough examination of every individual is therefore only achievable in clinical and small epidemiological studies. However, the major methodological problems are to quantify the exposure, standardise the allergen preparations used in inhalation challenges, and establish the IgE antibody sensitisation to the allergen, either with skin testing or serum assays for IgE antibodies or for other antibodies.

Different methods have been used to sample airborne allergens, ie, gravity sampling, impactors, and suction devices, but also vacuum cleaning of surfaces has been used for indirect estimation of exposure. Methods varying greatly in specificity and sensitivity have been used for determination of the allergen content of the sample, ie, light microscopy, culture of spores, immunoassays, and measurements of enzymatic activity.

Determination of precipitating antibodies to an antigen can only be used to indicate that exposure to the antigen has taken place, not to establish the diagnosis of extrinsic allergic alveolitis per se.
4.7. Major research needs

There is a need for studies on the relationship between indoor air allergen levels and asthma and rhinoconjunctivitis. Such studies should include:

- cross-sectional studies of the general population and high risk populations such as children in damp homes, kindergartens or schools where the relationship between allergen sensitivity, allergen exposure, asthma, rhinoconjunctivitis and bronchial reactivity could be studied.

- case control studies on unselected patients.

- longitudinal studies on the relationship between exposure and symptoms in allergic individuals along with longitudinal studies of populations exposed to higher levels of allergens.

- studies on how to avoid or remove allergens in the indoor air.

- studies to find accurate and feasible methods of measuring allergens in the indoor environment, especially airborne allergens.

- improvement of building design and air filtration methods to prevent introduction, spread, and accumulation of allergens in the indoor environment.
5. CANCER AND EFFECTS OF IAP ON REPRODUCTION

A few indoor air pollutants, notably asbestos, radon and environmental tobacco smoke (ETS) have been associated with cancer. Very few studies have tried to evaluate whether IAP affects human reproduction.

5.1. Cancer and effects on reproduction associated with exposure to IAP

Lung cancer is the major cancer which has been associated with exposure to IAP (radon or ETS). Asbestos exposure has been linked to cancer in workers and also in workers’ family members, presumably due to asbestos fibers brought into the home on workers’ clothing. However, there are no studies associating asbestos exposure in homes or public buildings from asbestos used as a construction material to the development of cancer. Effects on human reproduction have been associated with exposure to chemicals in the environment, but it is as yet unclear to what extent (if any) exposure to IAP is involved.

5.2. Principle agents and sources

The principle agents present in indoor air associated with lung cancer are ETS and radon decay products. Tobacco smoke has been known to cause cancer in man for a long time, and although sidestream smoke has a different composition from the mainstream smoke which is being inhaled by a smoker, carcinogens have been identified in sidestream smoke as well, and some investigations suggest that the concentration of carcinogens in sidestream smoke is higher (relative to other substances) than in mainstream smoke. It is well known that in smokers’ homes, the long term average concentration of particulate matter in the air is considerably higher than in non-smokers’ homes. Often, the concentration in smokers’ homes is also higher than in outdoor air. Few studies have measured carcinogens resulting from tobacco smoking in indoor air.

Radon and radon decay products can be present in high concentrations in homes built on soils which are rich in uranium. In several countries, areas have been identified in which indoor radon concentrations in homes approach levels which have been associated with an increased lung cancer incidence in miners. An overview of radon levels measured in homes in EC countries is given in the report "Radon in Indoor Air". Of interest are, particularly, the short-lived decay products Polonium-218 and Polonium-214; both of which attach to particulate matter in the air so that they can be deposited in the lungs. This is especially important when the particle load in indoor air becomes large, e.g., when there is tobacco smoking in the home. Effects of radon might therefore be more severe in smokers’ homes. In miners, radon exposure and smoking have been shown to act synergistically.

Of potential further interest are asbestos, polycyclic aromatic hydro-carbons, benzene, formaldehyde, some pesticides, and nitrosamines which may form on filters of recirculating kitchen exhaust fans, all of which have been found in indoor air, and all of which are known or suggested to be human carcinogens. However, there are no firm indications that the levels of these pollutants normally encountered indoors warrant
much concern. This is also true for exposure to electromagnetic fields, such as those generated by electric conductors.

Some chemicals which have been associated with adverse effects on human reproduction are tobacco smoke, solvents, chlorinated pesticides, and metals such as lead. Although most of these may occur in indoor air, there is, apart from ETS, basically no information to decide whether the levels normally encountered in indoor air warrant concern.

5.3. Evidence linking IAP to cancer and effects on reproduction in humans

Although several of the substances mentioned in the previous section are considered to be human carcinogens by the International Agency for Research on Cancer, only few of them have been linked to human cancer in epidemiological studies on specific indoor exposures. The main emphasis in these studies has been on the relationship between exposure to ETS ("passive smoking") and lung cancer, a topic on which a relatively large number of studies have been published. Although only a few of these show a significantly increased chance of dying from lung cancer associated with ETS exposure, several meta-analyses of all available information have concluded that the increase is real (US Surgeon General, 1986, UK Department of Health, 1988). The risk of dying from lung cancer associated with living with a smoker, relative to living with a non-smoker, has been estimated at 1.35. Most studies of the issue have considered (groups of adequate size of) women only, so that at present, it is not as clear to what extent non-smoking men living with a smoking partner are at increased risk.

The carcinogenicity of radon decay products for humans has been firmly established in studies among miners, at exposure levels exceeding those commonly found in the air in homes. Recently, some epidemiological studies have addressed radon in homes more directly, and some (but not all) of these suggest that exposure to radon decay products in the home is indeed associated with an increased lung cancer incidence. One case-control study from Sweden included measurement of indoor radon concentrations in the homes where study subjects had actually lived, and a significant dose-response relationship was found for all histological types of lung cancer combined, and for small cell carcinoma in particular. In this particular study, the elevated risk was restricted to smokers, suggesting an interaction between smoking and radon decay product exposure, as has been found in the occupational studies among miners too. However, an interaction between "passive smoking" and radon decay product exposure has been suggested also.

From occupational studies, asbestos fibres are known to be able to cause cancer (mesothelioma and lung cancer) in humans. Several case reports have shown that asbestos carried home on workers’ clothes can lead to high exposures in the home, and some fatal mesothelioma cases among non-occupationally exposed partners have been documented. Due to the widespread use of asbestos in the past, many buildings contain asbestos in some form, and low-level exposures occur in these buildings. However, there is ongoing discussion on whether these low levels of exposure are associated with a sizeable increase in the risk of mesothelioma or lung cancer.
Benzene is a known cause of leukaemia in occupationally exposed humans and may be present in indoor air at low concentrations. A large recent study indicates that the main sources of benzene exposure to the general population are personal activities or sources inside the home. The most important of these, accounting for over half of the population exposure to benzene is smoking. Other important sources are exposure to ETS and to certain consumer products. However, a number of occupational studies with low exposure levels have failed to detect significant increase in leukaemias among the exposed workers, and it is questionable whether increased risks exist at the even much lower levels encountered in homes. There have been no studies to document this. In areas with much automobile traffic, ambient concentrations of benzene are probably higher than those encountered indoors.

The mutagenicity of indoor air, as measured by in vitro techniques (see below), has been studied by several investigators. Mutagenicity refers to the capacity of a substance to induce a permanent change in the amount or structure of the genetic material in an organism, resulting in a change in the phenotype characteristics of the organism. The alteration may involve a single gene, a block of genes, or a whole chromosome. Tobacco smoke is a major source of mutagens in the air in homes. In addition, wood smoke from fire places and fumes produced by cooking activity have been shown to increase the mutagenicity of indoor air.

Occupational studies have shown that exposure to lead, ethylene oxide and some pesticides can lead to effects on human reproduction such as spontaneous abortions, infertility and chromosomal aberrations. There is no evidence that at the lower levels of exposure to these chemicals normally encountered in the non-occupational indoor environment, hazards of this type exist. Smoking has also been implicated, but there is little evidence that passive smoking is associated with these effects too.

5.4. Susceptible groups

Susceptibility to cancer is believed to vary among individuals due to genetic factors. However, methods so far available do not allow susceptible individuals to be reliably identified.

5.5. Public health relevance

Many non-smokers are exposed to ETS in the home, so the public health relevance of an increased lung cancer risk associated with ETS exposure are potentially large. In some countries, large numbers of homes have elevated levels of radon decay products in the air, and the risks estimated to be associated with these levels are sometimes appreciably higher than those deemed maximally acceptable for other chemical exposures. For example, the lifelong risk of developing lung cancer due to exposure to a radon decay product equilibrium concentration of 1 Becquerel/m$^3$ has been estimated by WHO (1987) at 0.7 - 2.1 per 10,000. In countries such as Sweden, Norway and Finland, many homes can be found with indoor concentrations exceeding 100 Bq/m$^3$, and those living in these homes therefore are exposed to an increased level of risk. In several countries, risks for life-long exposure to environmental carcinogens in the order of one per million only are considered
acceptable, which makes clear why exposure to indoor radon decay products has become such a prominent issue in the past decade.

ETS and radon may account for a sizeable fraction of lung cancer cases among non-smokers. As mentioned before, radon may, through synergistic interaction, account for a sizable number of lung cancer cases among smokers as well. For other human and animal carcinogens found in indoor air, there is insufficient epidemiological evidence to date to decide to what extent these are of concern at the levels which are normally encountered.

Data at present are insufficient to assess the public health relevance of potential effects of IAP on human reproduction.

5.6. Methods for assessment of carcinogenic effects and effects on human reproduction

The carcinogenicity of substances can be studied in animal experiments but usually, relatively high doses are required to induce cancer in a sufficient number of animals in the exposed groups. As a consequence, assessment of risk for humans from such data not only requires extrapolation from experimental animals to humans, but also from high to low doses. The uncertainty involved in both extrapolations is large. As a consequence, no reliable and precise estimate can be made of the cancer risks associated with human exposure to the substance on the basis of animal experiments alone.

The mutagenicity of substances can be tested using a variety of in-vitro and in-vivo tests. Bone marrow assays for chromosome damage are an example of the latter, the well-known Ames test is an example of the former. A mutagen is not necessarily a carcinogen, and by themselves, tests of mutagenicity do not permit risk assessment of human exposure.

Epidemiological studies can be used to detect whether human exposure to a substance is actually associated with an increased cancer incidence. Usually, large numbers of people need to be followed for a long time to unequivocally document changes in cancer incidence to be associated with exposure. Therefore, the case-control approach is widely used in cancer epidemiology, in which cancer cases are compared to suitable control subjects with respect to past exposure to the suspected agent and to other potential causes of cancer. In both types of study, confounding factors may produce spurious associations (or mask true associations) between exposure and disease, so that suitable treatment of confounders is a major issue.

Various specific approaches are used in toxicology to detect effects of chemical substances on reproduction. Among these are in-vitro tests on whole embryo systems, and mammalian three generation studies in which three consecutive generations of experimental animals are exposed to various dose levels of the substance under study. Human epidemiological studies have utilised study endpoints such as spontaneous abortion frequency, number of miscarriages, birth weight, sperm counts etc.
5.7. Major research needs

Several human carcinogens have been identified in indoor air, and although the levels of most of these are low, uncertainty remains about the actual health risks associated with most of these exposures. It can be argued that known carcinogens should not be present in indoor air and that consequently, efforts should be made to remove them from it. Such actions would provide opportunities for intervention-type studies, in which the consequences of remedial actions for the carcinogenicity and mutagenicity of indoor air are investigated.

The presence of several animal carcinogens and/or mutagens in indoor air, albeit at low levels, raises the question whether these mixtures could be harmful to humans. The potential carcinogenicity of representative, well defined mixtures should be further evaluated. In addition, human exposure to carcinogens and mutagens in indoor air should be better characterised, so that more reliable risk assessments can be made. To this end, further development of methodologies for risk assessment is necessary as well.
6. EFFECTS OF IAP ON THE SKIN AND MUCOUS MEMBRANES IN THE EYES, NOSE AND THROAT

6.1. Irritative effects associated with IAP

Exposure of the skin or mucous membranes to indoor air pollutants may cause effects on the sensory system and may result in tissue changes. Each of these may subsequently lead to the other. Two types of sensory irritation, therefore, appear in the literature on indoor climate and air quality: A primary sensory irritation caused by direct stimulation of sensory cells by environmental exposures and a secondary irritation following changes in the skin, mucous membranes or other tissues.

This chapter deals with irritative effects associated with tissue changes while primary sensory irritation will be dealt with in chapter 7. Inflammation is characterised by a sensation of heat ("calor"), redness ("rubor"), swelling ("tumor"), pain ("dolor") and a certain loss of function in the tissues affected. Irritative effects on tissues can be a considerable annoyance either in terms of severity of effects on an individual or in terms of the number of persons affected. Host factors such as hyperreactivity may play a role. Signs and symptoms of effects on skin and mucous membranes may appear at the site of contact on the exposed skin, mucosa etc. or manifest themselves in other tissues due to reflexes. Irritative effects causing tissue changes in the skin and mucous membranes have been reported in many forms, although they have seldom been seen to follow exposure to normal indoor air. The symptoms and signs are often unspecific and each may be caused by several different exposure factors. Also, some exposures may cause a number of different signs and symptoms. The most frequent effects related to indoor air quality seem to be acute physiological or sensory reactions, psychological reactions and subacute changes in sensitivity to environmental exposures.

6.2. Principle agents and sources related to irritative changes of mucosal tissues and skin

Formaldehyde: Formaldehyde is highly water soluble and causes irritation of the mucous membranes of the eyes and upper respiratory tract. Symptoms of irritation include a dry and/or sore throat and a tingling sensation of the nose, usually co-existing with watering and painful eyes. Irritation occurs over a wide range of concentrations, usually beginning with sensory irritation at approximately 0.1 ppm, but reported more frequently at or above 1 ppm. Increased tearflow and eye-blinking is reported to be caused by formaldehyde. At high exposure levels formaldehyde may act as an allergen and provoke IgE antibodies. Oedema and inflammation are known to appear after high levels of formaldehyde exposure exceeding normally occurring indoor air concentrations. Other aldehydes: acetaldehyde, acrolein and other aldehydes are known irritants. Their relation to irritation of the skin and mucous membranes in indoor environments has, however, not yet been extensively investigated. ETS is a major source of exposure to these compounds. Acrolein may produce conjunctivitis.

Volatile organic compounds (VOC): many VOC are mucous membrane irritants and VOC have been implicated as a cause of SBS. Studies of the acute effects of
VOC indicate that concentrations of VOC found in new buildings may cause irritative tissue changes in the eyes.

ETS is a complex mixture of pollutants whose source is primarily cigarette smoking. Various components of this mixture have been actively monitored, including respirable suspended particles, CO, nicotine, nitrogen oxides, acrolein, nitroso compounds and benzo(a)pyrene. The major sites of irritative changes caused by ETS are the eyes and nasopharynx. Eye and conjunctival irritation, nasal discomfort, sore throat, sneezing, and cough are frequently reported symptoms. Increased tearflow and eye-blinking are also reported to be caused by ETS.

Other exposures: the intensity of symptoms due to irritative effects may vary due to interactions with other exposures. Temperature and humidity have been demonstrated to influence the level of eye and nose irritation experienced by non-smokers exposed to ETS. Changed mucosal clearance is known from exposure to NOx or particulate matter. Irritation due to agents such as biological contaminants, or due to other factors have not been described in the literature to the level where a conclusion can be drawn.

6.3. Evidence linking exposure to IAP to irritative tissue changes

Apart from formaldehyde and ETS, chemicals which are likely to produce irritative changes are found at levels in the normal indoor environment which are orders of magnitude below those known to produce irritation in the industrial indoor environment. Few other agents are known to cause irritative effects at the concentrations found indoors. However, the effects observed in industrial environments may be different from the effects in the non-industrial indoor environment.

Most experimental studies of non carcinogenic effects of potential irritants do not involve exposure periods longer than a few hours and may therefore not show a relation between long term exposures and health effects.

Several experimental studies of the acute effects of VOC have been undertaken to study building related illness etc. These experiments have shown irritative effects of VOC at exposure levels encountered in new buildings, but interpretation of these studies is limited by the non specificity of the effects. The nature of the relationship between VOC exposure and building related illness or SBS remains unclear.

6.4. Susceptible groups

There appears to be a wide range of individual susceptibility to formaldehyde exposure. The exact proportion of people with increased susceptibility to formaldehyde is unknown.

Very few investigations have dealt with increased susceptibility to irritation due to indoor air pollutants other than formaldehyde. No conclusion can therefore be made with respect to the existence of other riskgroups.
6.5. Public health relevance of irritative tissue changes

Studies have been undertaken to determine the magnitude and extent of formaldehyde exposure of the general population in the home environment. Most studies have dealt with specific problems such as mobile homes, so that the results cannot be extrapolated.

The effects of other factors and their interactions - such as cigarette smoking history, variability of health status, gender, age and genetic predisposition (which may modify responses to formaldehyde) - have not been adequately evaluated. This makes it difficult to accurately assess the health risks due to irritative effects attributable to exposure to formaldehyde indoors.

More than half of the population is estimated to be exposed to formaldehyde as a component of ETS. Even though dose-response effects for irritative tissue change are not known, this exposure may be of public health concern.

Other exposures have been even less well characterised.

6.6. Methods for assessment of irritative effects

The possible effects of indoor air pollutants on the skin and mucous membranes can be measured at high exposure levels. The available methods have strongly varying sensitivities, precisions and accuracies. Most objective methods have not yet been documented to work at exposure levels relevant to the non-industrial indoor environment and there is a general need for development and validation of such methods. Objective measurements of irritation of the eyes are at present the most promising.

Animal models are available for evaluation of the potential of chemicals to cause irritative effects and they are currently used in experimental chemical testing. However, these tests have not been used so far at exposure levels normally occurring in the indoor environment and the validity of extrapolations from the results of such animal tests to such level exposures of humans still needs to be demonstrated.

As few validated objective methods exist to document effects that may be caused by low exposure levels in humans, "markers" or substitute measures of irritative effects are being used. Irritation of the eyes may be measured as changes in the chemical composition of the eye fluids. There are some indications of a changed tearfilm break-up time following exposure to irritants. Irritation of the nose may be monitored as a changed mucociliary flow rate or a changed chemical composition of the nasal fluids.

Only a few markers of irritative effects at pollution levels known from indoor air are available, and most of them are still at the developmental stage.
6.7. Major research needs

Irritative changes at exposure levels known to occur in indoor non-industrial environments are not well documented except for a few compounds or sources, notably formaldehyde and ETS. Many other exposure factors are known to cause irritation at higher exposure levels, but their postulated effects at non-occupational indoor environment exposure levels are difficult to measure due to interference from other exposure factors or interactions from many co-factors related to both exposure and personal sensitivity. A priority in research therefore is to test the irritative potential of these exposure factors at relevant exposure levels in combination with other co-factors. Such tests are difficult to perform due to low sensitivity and low specificity of the available measuring methods for irritative effects or markers. Development of new methods therefore should take place before major campaigns are initiated to measure irritation. This development should include methods for identification of groups at risk.
7. SENSORY EFFECTS AND OTHER EFFECTS ON THE NERVOUS SYSTEM DUE TO IAP

7.1. Sensory effects and other effects on the nervous system associated with IAP

Sensory effects are defined within the context of this report as the perceptual response to environmental exposures. Sensory perceptions are mediated through the sensory systems. These systems all contain various receptors, from which signals are transmitted to the higher levels of the CNS where the message results in a conscious experience of smell, touch, itching, etc.

Sensory effects are typically observed in buildings with indoor climate problems because many chemical compounds found in the indoor air have odorous or mucosal irritation properties. It is important to notice that most indoor air chemicals with a measurable vapor pressure will be odorous when the concentration is high enough. Some compounds will be odorous even at concentrations far below their analytical detection limit. The odor of others may only be detectable at concentrations exceeding the thresholds for other adverse health effects.

Sensory effects are important parameters in indoor air quality control for several reasons. They may appear as: (1) adverse health effects on sensory systems (e.g., environmentally-induced sensory dysfunctions); (2) adverse environmental perceptions which may be adverse per se or constitute precursors of disease to come on a long term basis (e.g., annoyance reactions, triggering of hypersensitivity reactions); (3) sensory warnings of exposure to harmful environmental factors (e.g., odor of toxic sulfides, mucosal irritation due to formaldehyde); (4) important tools in sensory bioassays for environmental characterization (e.g., using the odor criterion for general ventilation requirements or for screening of building materials to find those with low emissions of volatile organic compounds).

In the indoor environment, two main classes of sensory perception can be identified. The first class includes perceptions attributed to the surrounding physical environment (environmental perception), for example perceptions of draft and odor. Environmental perceptions can be adverse or non-adverse. The second class includes perceptions of events inside the body or on the body surface (body perceptions). The body perceptions, for example perceived eye irritation or dry skin, may or may not be attributed causatively to the surrounding physical environment. The sensory systems are tuned towards registering environmental changes rather than the absolute levels. The senses responding to environmental exposure are not only hearing, vision, olfaction and taste, but also the skin and mucous membranes. As pointed out by WHO (1989), many different sensory systems that respond to irritants are situated on or near the body surface. Some of these systems tend to respond to an accumulated dose and their reactions are delayed. On the other hand, in the case of odor perception the reaction is immediate but also very much influenced by olfactory fatigue on prolonged exposures.

Responders are often unable to identify a single sensory system as the primary route of sensory irritation by airborne chemical compounds. The sensation of irritation is influenced by a number of factors such as previous exposures, skin temperature,
competing sensory stimulation, etc. Since interaction and adaptation processes are characteristic of the sensory systems involved in the perception of odor and mucosal irritation, the duration of exposure influences the perception.

Humans integrate different environmental signals to evaluate the total perceived air quality and assess comfort or discomfort. Comfort and discomfort by definition are psychological and for this reason the related symptoms, even when severe, cannot be documented without using subjective reports.

Sensory effects reported to be associated with IAP are in most cases multisensory and the same perceptions or sensations may originate from different sources. It is not known how different sensory perceptions are combined into perceived comfort and into the sensation of air quality. Perceived air quality is for example mainly related to stimulation of both the nerves trigeminus and olfactorius. Several odorous compounds are also significant mucosal irritants, especially at high concentrations. The olfactory system signals the presence of odor compounds in the air and has an important role as a warning system. In the absence of instrumentation for chemical detection of small amounts of some odor compounds, the sense of smell remains the only sensitive indicator system.

It is well known that environmental pollution can affect the nervous system. The effects of occupational exposure to organic solvents can be mentioned as an example. A wide spectrum of effects may be of importance, ranging from those at molecular level to behavioral abnormalities.

Since the nerve cells of the CNS typically do not regenerate, toxic damage to them is usually irreversible. The nerve cells are highly vulnerable to any depletion in oxygen supply. Furthermore, the nerve cells will be exposed for a long time to chemicals that are able to enter the CNS. The risk of accumulation of hazardous compounds within the CNS is higher than in most other body tissues since the nerve cells are slow in metabolizing intruding chemicals. Many solvents affect the nerve cells or the transmission of nerve signals, e.g., by inducing narcotic effects.

Although a number of adverse health disorders of the CNS, like Parkinson's disease and Alzheimer's disease are suspected to be associated with exposure to hazardous pollutants in the environment, there is at this moment no documentation that would implicate non-industrial exposure in homes or offices to IAP as being related to these endpoints.

7.2. Principle agents and sources

Sensory effects have been linked to various indoor air pollutants. In particular, many organic compounds may cause odors and/or mucosal irritation at concentrations encountered indoors. Formaldehyde is a strong mucosal irritant and the most common pollutant occurring in the indoor air at concentrations known to cause sensory irritation in the eyes and respiratory tract. These symptoms have been reported in buildings with particle board or Urea Formaldehyde Foam Insulation (UFFI) after remodeling or after installation of new furnishings or carpets.
A great number of volatile organic compounds are emitted from indoor materials and products. Many indoor materials, including paints, stains, adhesives, and caulks contain petroleum-based solvents. Such solvents are composed of a variety of organic compounds which often subsequently are found in indoor environments.

Volatile organic compounds enter the indoor environment also from cigarette smoke and from unvented combustion appliances. Not all of these substances have been identified. However, environmental tobacco smoke is known to produce sensory irritation and odor complaints, and it therefore contributes to the perception of bad indoor air quality.

Effects on the nervous system can be produced by several agents present as pollutants in the indoor environment which are known to be neurotoxic but of which effects generally have only been shown at high exposure levels in occupational settings.

The most important of the potentially neurotoxic substances found in the indoor air are the volatile organic compounds, VOC. They include acetone, benzene, toluene, cyclohexane, n-hexane, formaldehyde, styrene, chlorinated solvents, and several other organic solvents. Another compound causing adverse CNS effects, which can be fatal, is carbon monoxide (CO), which may interfere with oxygen supply of the nervous tissue. Impaired vigilance function is one of the possible effects.

Some pesticides are also well known neurotoxins. Most are poisonous to insects and parasites because of their neurotoxicity and may act on mammals through the same mechanisms. Prolonged exposure to some pesticides may cause irreversible effects in the central or peripheral nervous system. The extent of exposure to these chemicals in indoor environments are not clear and vary much according to geographical areas, proximity to agricultural settings and local habits of use of pesticides.

7.3. Evidence linking IAP to sensory effects and effects on the nervous system

As mentioned above, many indoor air pollutants are odorous, and there is ample evidence that sensory effects of indoor air pollutants are playing an important role in the occupant's acceptability of indoor air quality. Furthermore, sensations are the integrated net response of the body to a large number of interacting components and the effects appear at an early stage. However, it should be noted that some air pollutants lack sensory warnings and behave differently from the odorous ones.

One of the important characteristics of an odorant or irritant is the concentration at which it can be barely detected by a subject (detection threshold) or recognized (recognition threshold). However, reported detection and recognition threshold data can vary by up to four orders of magnitude between studies from different laboratories using different measuring techniques. Very little information is available about dose-response relationships of airborne mucosal irritants, somewhat more of odors.
Exposures to neurotoxic substances may lead to a large variety of effects on the nervous system from the very subtle, e.g., aberrant social behavior, to the severe, for example, paralysis. It is often very difficult to demonstrate evidence of neurotoxicity.

As mentioned, effects on the nervous system have not often been linked to exposure to IAP. Practically all organic solvents are able to interfere with nervous system functions in man at high concentrations. However, the exposures associated with neurotoxicity are generally some orders of magnitude higher than exposures usually encountered in nonindustrial indoor environments.

Controlled human exposures to complex mixtures of VOC have suggested the possibility of functional memory impairment and sensory irritation at concentrations comparable to those detected in newly constructed buildings. These studies, moreover, showed effects at a range of concentrations at which such effects would not have been predicted on the basis of existing toxicological information in the literature. This calls for extensive research on the possible interaction effects of the single components of mixtures.

Interference of carbon monoxide with the performance of complex sensori-motor tasks or with functions such as visual perception, manual dexterity and ability to learn has been demonstrated to occur at carboxyhemoglobin levels between 5 and 17% in several human studies. It cannot be excluded that such effects may appear at lower levels in susceptible subjects. Concentrations of carboxyhemoglobin associated with effects on the CNS are of the same order of magnitude as those reported to occur in some indoor environments polluted by sources like improperly ventilated or adjusted combustion appliances.

The neurotoxicity of several pesticides is well documented from animal studies. Human investigations are few and their results are not always easy to interpret. Specific investigations on the neurotoxic potentials of non-industrial, indoor pesticide exposure are lacking.

7.4. Susceptible groups

There are large differences in sensory sensitivity between individuals as demonstrated for vision, hearing, and olfaction. By aging the sensitivity is known to decrease in most individuals. Foetuses and children are particularly at risk for neurotoxic effects as a result of the higher life-time exposure and of the sensitivity of the brain during its growth stages.

7.5. Public health relevance

As pointed out by WHO (1987), in their Air Quality Guidelines for Europe, many substances in the indoor environment may cause sensory effects at concentrations far below those at which toxic effects occur. Also, sensations are the integrated net response of the body to a large number of interacting components and the effects appear at an early stage. Some pollutants lack sensory warnings and behave differently from the sensorily stimulating ones, precluding the sole use of sensory
perception as an indicator effect. In these cases, the pollutants must be controlled by other means.

An example of an assessment of human health risks based on sensory criteria is the WHO (1989) document on environmental health criteria for formaldehyde. The argument applied is that human exposure to formaldehyde should be minimized not only for its probable carcinogenic effect, but also for its potential to cause irritation. WHO recommends that in order to avoid strong sensory reactions in workplace environments where formaldehyde is being produced or used, peak concentrations above 1.0 mg/m$^3$ should not be allowed and mean concentrations should be kept below 0.3 mg/m$^3$. With regard to exposure outdoors and in the non-industrial indoor environment, the formaldehyde concentration should not exceed 0.1 mg/m$^3$ in order to avoid odor and sensory irritation for the general population. In the case of specially sensitive groups, that show hypersensitivity reactions without immunological signs, formaldehyde concentration should be kept to a minimum and should not exceed 0.01 mg/m$^3$.

The prevalence of neurotoxic effects in the population as a result of indoor exposure to neurotoxic air pollutants is difficult to estimate. It is true, though, that several indoor air pollutants are potentially neurotoxic at high exposure levels either as single compounds or in mixtures or in combination with other environmental factors. There is no documentation of neurotoxic effects clearly linked to indoor exposure.

A large part of the general population is exposed to low concentration of VOCs. Some individuals may experience higher exposures during indoor use of certain products or after furnishing or home redecoration. Carbon monoxide exposure may be important depending on the type of heating and combustion appliances in use and on the ventilation of the building.

Pesticide exposure may be a risk factor in homes located in rural areas, as well as in other homes where pesticides have been used indoors. Pentachlorophenol, a neurotoxic wood preservant has been measured at elevated concentrations in the urine of subjects living in houses with indoor wood surfaces even 10 years after the application of this chemical.

7.6. Methods for assessment of effects

Sensory effects such as odor and mucosal irritation are perceptions and therefore by definition subjective in nature. The assessment of such subjective aspects of sensory stimulation must involve humans. The olfactory system adapts during prolonged exposure and olfactory measurement should control for this adaptation. As a consequence of adaptation to any odor in indoor air, two different responses may be identified: that of the visitor and that of the occupant. A WHO expert group has recommended that odors should be measured through the immediate response of the unadapted olfactory system (visitor situations). It should be noted that odor intensity measured by visitors does not necessarily correlate with the perceptions of the occupants.
A number of indicators or substitute measures may be used to estimate or predict the odor or mucosal irritation potency of chemicals. The concentration of total volatile organic compounds has been suggested as a possible indicator of the overall perceived indoor air quality. Carbon dioxide emitted by human metabolism is often used as an indicator for perceived indoor air quality as affected by bioeffluents.

The science of psychophysics offers a variety of sensory models for studying indoor air quality effects and for indoor air quality characterization (bio-assays). Regulatory agencies now require sensitivity, validity, reliability and biological meaningfulness of sensory methods applied for indoor air quality control. Therefore, quality assurance in sensory measurements is mandatory.

Individuals, panels and populations do differ in sensory sensitivity, response behavior and value judgements. Some of these differences are environmentally induced. It is important to specify the target groups of indoor air quality control based on sensory effects and how they relate to large population groups.

Methods for assessing neurotoxicity in animal and human studies include a number of neurophysiological and behavioral diagnostic techniques designed to study selected central or peripheral nervous functions. Examples of neurobehavioral tests are reaction time, memory, manual dexterity, etc., and examples of electrophysiological techniques are measurements of visual or auditory evoked potentials, nerve conduction velocity, etc. These tests are increasingly being used in the field because of their noninvasive nature. Neurobehavioral tests can be used in experimental laboratory settings as well as in epidemiological studies. However, the attribution of abnormal results to acute reversible impairments or to irreversible brain lesions may be difficult.

7.7. Major research needs

There are still major difficulties in predicting sensory effects and effects on the nervous system of chemicals at commonly encountered indoor concentrations, especially the early, subtle and reversible effects. There is a need for biological indicators for monitoring such effects and particularly for identifying:
- adverse effects at realistic exposure levels (low-dose effects)
- the vulnerable portions of the general population, and
- the combined effects of pollutants and other environmental factors, and of physiological and toxicological reactions in the human body.

A ranking system is needed for building and consumer products based on harmonized test procedures including tests for sensory and neurological effects. Fast screening procedures should be developed for appropriate end-points of health and comfort. Sensory tests, for example for odor, may be used for fulfilling part of this purpose.

Many threshold limit values for occupational health purposes are based on irritant properties of the chemicals. The occupational limit values are set high since they are aiming only to protect healthy, adult workers but not individuals who may be more susceptible due to their age or health status.
Increased emphasis should be given to research on the sensory effects in humans of chemical compounds in the low concentration ranges as encountered in nonindustrial indoor environments. This is especially true for detection and recognition data which should be collected in a way which allows the full dose-response curve to be determined.

The detection limit of presently used analytical instruments is in many cases higher than that of the human sensory systems. Therefore, many strong odorants have not yet been chemically identified. To arrive at prediction models for the sensory potency of complex mixtures, controlled human exposure studies should be made with realistic pollutant mixtures. Human experimental exposure to complex indoor mixtures may lead to identification of mixtures of particular interest, unforeseen interaction among chemicals, and concentrations at which interference with nervous functions occurs.

Very little is known about the extent of neurotoxic effects of non-industrial indoor pollution, and further work (i.a., epidemiologic studies) is indicated to evaluate the possibility that these effects will occur. A distinction has to be made between transient, reversible effects and irreversible, persistent neurotoxic impairments. More data are needed on population exposure to pesticides. This group of chemicals may be persistent contaminants of indoor spaces. Routes of exposure other than inhalation also need to be taken into consideration for these substances as well as for VOCs.

Last but not least, methods for identification of susceptible subjects experiencing the effects discussed in this chapter at much lower concentrations than others need to be developed.
8. EFFECTS OF IAP ON THE CARDIOVASCULAR SYSTEM

Cardiovascular effects have only infrequently been described as being associated with exposure to IAP. Only exposures to ETS and carbon monoxide (CO) have been implicated in cardiovascular symptoms, and in changes in Cardiovascular Disease (CVD) morbidity and mortality.

8.1. Cardiovascular effects associated with IAP

Increased mortality due to CVD has been associated with exposure to ETS in some groups of non-smoking women married to smokers. Some investigators have also addressed the question whether total mortality is influenced by exposure to ETS, but results have been contradictory. As any effect on mortality would not be expected to occur until after many years of exposure, a problem in these types of study is the accuracy and reliability of the exposure classification. Attempts have also been made to relate ETS to electrocardiographic abnormalities and cardiovascular symptoms, but results have been inconclusive.

Carbon monoxide (CO) exerts its influence primarily through binding to the haemoglobin (Hb) in blood. The affinity of CO to Hb is about 200 times higher than the affinity of oxygen to Hb, so that at relatively low levels of CO in the air, oxygen is replaced by CO. The percentage of Hb bound to CO (% carboxyhaemoglobin) is a measure of recent exposure to CO. Organs with a high oxygen demand, such as the heart and the brain, are particularly susceptible to a reduced oxygenation caused by CO exposure. Early effects include reduction of time to onset of chest pain in exposed, exercising heart disease patients. At higher levels of exposure, myocardial infarctions may be triggered by CO.

8.2. Principle agents and sources

ETS and carbon monoxide (CO) are the main components of indoor air that have been associated with cardiovascular effects. Active smoking is a well known cause of cardiovascular disease. Carbon monoxide present in tobacco smoke is one of the likely causal agents, as smokers are known to have chronically elevated levels of carboxyhaemoglobin in their blood. Whether or not CVD effects resulting from exposure to ETS are related to CO is questionable, as CO concentrations are not very much elevated by tobacco smoking unless ventilation is restricted. Non-smokers exposed to ETS generally do not have significantly elevated levels of COHb in their blood.

Exposure to lead in the general environment has been related to high blood pressure in adults, but exposure of adults to lead is mostly through the food chain, and not so much via indoor air.

8.3. Evidence linking IAP to effects on the cardiovascular system

Few studies have addressed the issue of IAP and CVD, although some epidemiological studies have addressed the relationship between exposure to ETS and mortality and morbidity due to CVD. As discussed in recent, major reviews (US
Surgeon General, 1986, Samet et al., 1987/1988), the evidence obtained from these studies is limited or inconclusive. However, recent cohort studies among non-smokers have suggested that living with a smoker is associated with a significantly increased relative risk of dying from CVD.

The effects of CO on cardiovascular symptoms such as time to onset of aggravation of angina symptoms in angina pectoris patients have been well documented in human studies.

8.4. Susceptible groups

Persons with angina pectoris or with obstructed coronary arteries should be considered to be a susceptible group. Other susceptible groups are those with disorders (e.g. anaemia) which reduce the oxygen carrying capacity of the blood.

8.5. Public health relevance

Many people are exposed to ETS. CVD is a major cause of morbidity and mortality in most developed countries. Even when relative risks are moderate, the number of people which could be affected by ETS in this respect is potentially large. The final assessment of the public health relevance awaits conclusive studies of this issue.

CO levels indoors do not usually exceed recommended levels as published by WHO (1987). Therefore, the public health relevance of indoor CO pollution in causing or aggravating CVD is probably limited. Nevertheless, CO is known to reach high levels in some homes when a number of unfavourable circumstances combine. Effects of CO are unspecific and may go undetected by physicians and other health professionals. It is considered by some to be "an old enemy forgot", and it is one of the few indoor air pollutants that kills several hundred and possibly thousands of Europeans each year.

8.6. Methods for assessment of effects on the cardiovascular system

The main study types, mentioned in chapter 2, are applicable here as well. Mortality studies typically rely on death certificates which may not always contain the correct diagnosis. Morbidity studies use symptom questionnaires, ECG measurements, measurement of serum cholesterol and of blood pressure. CVD has been the subject of an extremely large number of studies, and the methods to investigate symptoms and physiological and biochemical variables are well developed and standardised.

8.7. Major research needs

Few studies have considered CVD as an endpoint of exposure to IAP. Exposure to ETS especially is in need of further evaluation as a potential risk factor for developing CVD, given the large public health impact of CVD in modern, industrialised societies.
9. SYSTEMIC EFFECTS OF IAP ON THE LIVER, KIDNEY AND GASTROINTESTINAL SYSTEM

9.1. Systemic effects associated with IAP

Systemic effects are defined as biological effects on one or more target organs caused by absorption and distribution of a toxic agent within the body. They include effects such as gastrointestinal, hepatic or renal effects, some immunosuppressive effects on organs and a group of miscellaneous effects. Such systemic effects have never been documented but have only been suggested in relation to IAP. At present no firm evidence exists for a causal link between these effects and exposure to non-industrial, IAP.

The gastrointestinal tract is the first system in contact with chemicals contained in food and drinks. In addition, through the liver and biliary system, the gut provides a route for excretion of toxic chemicals, drugs, and products of metabolism. More important, in relation to indoor air, is the secondary swallowing of pollutants originally trapped in the airways (mucociliary clearance) and then transported to the throat. Due to transportation time in the body and dilution of the pollutant in body fluids, few acute systemic effects are expected as a result of exposure to the low levels of pollutants occurring indoors. The main effects, if they exist, would be expected to be subchronic or chronic.

9.2. Principle agents and sources

Gastrointestinal system: Gastrointestinal symptoms caused by inhalation of toxic substances in normal indoor air have not been documented.

Hepatic effects: These effects have been related to pesticides and other organic compounds such as pentachlorophenol applied in and around buildings to control insects or microbiological growth. Investigations have not been extensive and reliable exposure estimates or exclusion of other potential causes were lacking in the cases reported. Hepatotoxic effects would be possible from other types of organics, such as halogenated VOC. No epidemiological work has, however, been performed to relate exposures to such health effects.

Renal effects: Renal damage can be caused by many chemical compounds. Cadmium is among the most well known environmental contaminants linked to renal disease. No renal effects of exposure to normal indoor air have been documented.

Other health effects: ETS has been related to impaired growth and reduced general health of children exposed to it. Most studies, however, have been unable to differentiate effects of in utero exposure from childhood exposures to ETS. It has recently been suggested that non-smoking pregnant women exposed to ETS for several hours on a daily basis are at increased risk for producing babies of low birth weight.

Exposure to ETS in homes has been linked with increased incidence rates of chronic ear infections and middle-ear effusions in young children.
Studies on systemic immuno-suppressive effects of indoor pollutants are lacking.

9.3. Evidence linking exposure to IAP to systemic effects

The level of knowledge about systemic effects on humans due to indoor air is very low and, at present, does not allow conclusions about the risks associated with exposure to indoor air in normal non-industrial buildings.

9.4. Susceptible groups

There is no information about susceptible groups in relation to systemic effects caused by indoor air. It may be expected that groups showing hypersusceptibility to other types of environmental exposures causing systemic effects may be risk groups for exposure to the same compounds in the indoor air. Such groups will often be characterised by age, genetic factors such as sex or race, smoking habits, hypersensitivity status, general health conditions and occupation.

9.5. Public health relevance

No documentation was available to the working group describing the relevance of systemic effects caused by indoor air for public health.

9.6. Methods for assessment of systemic effects

There are several tests available for the detection of gastrointestinal diseases and some for the identification of persons at risk. The applicability of these methods for detection of possibly subtle effects associated with IAP has yet to be documented.

A great number of tests of hepatic function are available and could be tailored to the particular objective of any experimental or epidemiological study. Again, the applicability of these methods for detection of possibly subtle effects associated with IAP has to be documented.

The early stages of renal damage are seldom accompanied by symptoms. Thus, questionnaires are useless in the early detection of renal impairment, and laboratory tests are imperative. Such tests measure changes in urinary sediments and glomerular and tubular function.

9.7. Major research needs

Most of the questions related to the possibility of normal indoor air causing the type of systemic effects dealt with in this chapter are unanswered. Further research is needed to find out whether these effects, which are known from other types of exposures, may also be related to indoor air exposures.
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The report contains a summary discussion of human health effects linked to indoor air pollution (IAP) in homes and other non-industrial indoor environments. Rather than discussing the health effects of the many different pollutants which can be found in indoor air, the approach has been to group broad categories of adverse health effects in separate chapters, and describe the relevant indoor exposures which may give rise to these health effects. The following groups of effects have been considered: effects on the respiratory system; allergy and other effects on the immune system; cancer and effects on reproduction; effects on the skin and mucous membranes in the eyes, nose and throat; sensory effects and other effects on the nervous system; effects on the cardiovascular system; systemic effects on the liver, kidney and gastro-intestinal system. For each of these groups effects associated with IAP, the principal agents and sources, evidence linking IAP to the effect(s), susceptible groups, the public health relevance, methods for assessment, and major research needs are briefly discussed.