Project no. SSPE-CT-2004-502671

EnVIE

Co-ordination Action on Indoor Air Quality and Health Effects

Instrument: Co-ordination Action

Thematic Priority: Policy-oriented research (SSP)

Deliverable 1.1
WP1 Technical Report
Health Effects

Due date of deliverable: 15 December 2008
Actual submission date: 15 December 2008

Start date of project: 01/04/2004 Duration: 55 months

Organisation name of lead contractor for this deliverable: UMIL

Project co-funded by the European Commission within the Sixth Framework Programme (2002-2006)		
Dissemination Level		
PU	Public	PU
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

ENVIE
Co-ordination Action on Indoor Air Quality and Health Effects

WP1 Final Report

Health Effects

by

Paolo Carrer (WP1 leader), Occupational and Environmental Health, University of Milan, Italy

with

Anna Clara Fanetti, Dpt. Occupational and Environmental Health, University of Milan, Italy

Francesco Forastiere, Dpt. of Epidemiology, Local Health Authority, Rome, Italy

Ivana Holcatova, Charles Univ., Institute of Hygiene & Epidemiology, Prague, Czech Republic

Lars Mølhave, Dpt. of Occupational and Environmental Medicine, University of Aarhus, Denmark

Jan Sundell, Technical University of Denmark

Giovanni Viegi, Pulmonary Environmental Epidemiology Unit - CNR, Pisa, Italy

Marzia Simoni, Pulmonary Environmental Epidemiology Unit - CNR, Pisa, Italy

Table of contents

Executive Summary

Modern European citizens spend on average over 90% of their time indoors. Indoor air originates from outdoors, carrying outdoor air contaminants indoors with varying degrees of penetration. Also indoor environments contain sources of contaminants, which may lead to quite high exposure levels due to low indoor air exchange rates.

The combination of the generally higher indoor concentrations and the overwhelming fraction of time spent indoors results in the overall domination of indoor air in air pollution exposures – and their respective health consequences - regardless of whether the sources are indoors or outdoors. Different pathways from indoor sources lead to a broad variety of health outcomes that are attributable to the indoor environments.

Based on a review of the main important projects on indoor air related health effects, the following diseases have been prioritised as being caused or aggravated by poor indoor air quality: Allergic and asthma symptoms; Lung cancer; Chronic obstructive pulmonary disease (COPD); Airborne respiratory infections; Cardiovascular mortality and morbidity; Odour and irritation (SBS symptoms).

The most widespread and significant indoor pollutants associated with indoor related diseases have been identified. Policy options are proposed in order to prevent the onset of indoor related diseases. Policies should be focused on indoor exposures to identify, control and eliminate the indoor sources of pollution.

1. Introduction

Millions of Europeans spend more than 90% of their time indoors: at home, in the office, factory, school, restaurants, theatres, etc.

The combination of the generally higher indoor concentrations and the overwhelming fraction of time spent indoors results in the overall domination of indoor air in air pollution exposures and their respective health consequences. Indoor air pollution may cause or aggravate illnesses, increase mortality, and have a major economic and social impact.

European citizens want to live longer, healthier, in an environment of low involuntary risks, and at an affordable cost. Urban environmental policies should, therefore, manage the determinants of health as far upstream as possible and improve the citizens' quality of life. People are exposed to a multitude of chemical, physical and biological stressors in their environment, some of which are apparently harmless, others of low health significance and some incur significant risks to health, at least for vulnerable individuals. Human exposure to environmental contaminants occurs via various pathways (air, water, food, etc.) and routes of entry (inhalation, ingestion and dermal). Exposure via air occurs outdoors and in different indoor microenvironments; e.g. home, workplace, transit. Indoor air pollution from different sources may cause or aggravate illnesses, increase mortality, and have major economic and social impacts.

2. Objectives

The following issues were part of the present study:
- to provide a critical review and collection of European (and non-European) research on the health effects of indoor air relevant contaminants ;
- to assess the policy relevance of their objectives and conclusions;
- to evaluate the significance of indoor sources on the onset of asthma and allergy symptoms and the potential of building envelope and HVAC system to protect the susceptible individuals.

3. Materials and methods

The identification of the main health effects was performed by the review of the literature and on the results of some of the most important European and International projects/guidelines dealing with indoor air quality, including the following research studies/documents:

- ECA reports

In this series the following reports have already been published.

Report No. 1:	Radon in indoor air. EUR 11917 EN, 1988. *
Report No. 2:	Formaldehyde emission from wood-based materials: guideline for the determination of steady state concentrations in test chambers. EUR 12196 EN, 1989. *
Report No. 3:	Indoor pollution by NO2 in European countries. EUR 12219, EN1989.
Report No. 4:	Sick building syndrome - a practical guide. EUR 12294 EN, 1989.
Report No. 6:	Strategy for sampling chemical substances in indoor air. EUR 12617 EN, 1989.
Report No. 7:	Indoor air pollution by formaldehyde in European countries. EUR 13216 EN, 1990. *
Report No. 8:	Guideline for the characterization of volatile organic compounds emitted from indoor materials and products using small test chambers. EUR 13593 EN, 1991.
Report No. 9:	Project inventory – 2nd updated edition. EUR 13838 EN, 1991.
Report No. 10:	Effects of indoor air pollution on human health. EUR 14086 EN, 1991.
Report No. 11:	Guidelines for ventilation requirements in buildings. EUR 14449 1992, EN.
Report No. 12:	Biological particles in indoor environments. EUR 14988 EN, 1993.
Report No. 13:	Determination of VOCs emitted from indoor materials and products. Interlaboratory comparison of small chamber measurements. EUR 15054 EN, 1993.
Report No. 14:	Sampling strategies for volatile organic compounds (VOCs) in indoor air. EUR 16051 EN, 1994.
Report No. 15:	Radon in indoor air. EUR 16123 EN, 1995.
Report No. 16:	Determination of VOCs emitted from indoor materials and products: Second interlaboratoriy comparison of small chamber measurements., EUR 16284 EN, 1995.
Report No. 17:	Indoor air quality and the use of energy in buildings. EUR 16367 EN, 1996.
Report No. 18:	Evaluation of VOC emissions from building products –solid flooring materials., EUR 17334 EN, 1997
Report No. 19:	Total Volatile Organic Compounds (TVOC) in indoor air quality investigations. EUR 17675 EN, 1997
Report No. 20:	Sensory evaluation of indoor air quality, EUR 18676 EN, 1999.
Report No. 21:	European Interlaboratory Comparison on VOCs emitted from building materials and products, EUR 18698 EN, 1999.
Report No. 22:	Risk assessment in relation to indoor air quality, EUR 19529 EN, 2000.
Report No. 23:	Ventilation, Good Indoor Air Quality and Rational Use of Energy, EUR 20741 EN, 2003.
Report No. 24	Harmonisation of indoor material emissions labelling systems in the EU, Inventory of existing schemes, EUR 21891 EN, 2005.
Report No. 25:	Strategies to determine and control the contributions of indoor air pollution to total inhalation exposure (STRATEX), EUR 22503 EN, 2006

- INDEX project (Kotzias et al, 2005),
- SCHER opinion on indoor air (SHER, 2007)
- REPORT ON RISK ASSESSMENT ON INDOOR AIR QUALITY (2007)

It was reported that a number of factors in the indoor environment can affect well-being and health. The main factors include: chemicals for intended use or unintentional emissions from different sources (formaldehyde, carbon monoxide, nitrogen dioxide, benzene, lead and organophosphate pesticides), ETS, radon, particles, microbes, humidity, pets and pests.

- THADE project (Franchi et al., 2006),

- YEARLY DIRECT MEDICAL COSTS OF INDOOR RELATED DISEASES IN ITALY Italian National Commission “Indoor”, Minister of Health, (G.U. n. 276, 27/11/2001)
- US National Occupational Research Agenda on Indoor Work Environments (Mendell et al, 2002),

For the priority area “Indoor work environment” the team identified three types of heath effects as priorities for increased research, namely:

1. building-influenced communicable respiratory infections, due to occupant sources (e.g. influenza, common cold, tubercolosis) or building sources (Legionnaires’ disease, Pontiac fever, fungal infections);
2. building-related asthma, hypersensitivity pneumonitis and allergic diseases;
3. non-specific building-related symptoms (including so-called sick building syndrome).

- WHO working group on indoor air quality guidelines (WHO, 2007).

The working group outlined three tasks required for the guideline development in 2007-2009:

1.To list the specific chemicals for which numerical guidelines can be prepared

2.To assess the biological contamination of indoor air

3.To assess the effluents of indoor combustion of solid fuels.

4. Results

Based on this review the following diseases have been prioritised as being caused or aggravated by poor indoor air quality: allergic and asthma symptoms; lung cancer; chronic obstructive pulmonary disease (COPD); airborne respiratory infections; cardiovascular mortality and morbidity; odour and irritation (SBS symptoms).

4.1 Allergic and asthma symptoms

Respiratory allergies are very common and increasing throughout Europe.

They include asthma, allergic diseases and airway hyperreactivity. The impact of asthma on the life quality is particularly severe, but also the other allergic diseases, like allergic rhinitis should not be viewed as a minor irritation, as can cause a level of discomfort in the patient equivalent to that of moderate asthma.

Asthma affects between 3% and 8% of the adult population in Europe, and the prevalence is even higher in infants, in particular the ISAAC study reported that in children of the European centres involved in the study the prevalence of asthma symptoms ranged from 2.5 to 37%. For the period 1995-1996, the International Study of Asthma and Allergies in Childhood (ISAAC) found an 11.5% annual average prevalence of self-reported asthma symptoms in children aged 13–14 years Europe-wide. The rate ranges from 2.6–4.4% in Albania, Romania, Georgia, Greece and the Russian Federation to 29.1–32.2% in Ireland and the United Kingdom (Beasley, 2000).

Asthma places a high burden on the health care systems in many European nations. In the UK and Republic of Ireland, there are over 4 million primary health care consultations for asthma each year. In the Netherlands it has been estimated that the annual direct medical cost per person with asthma is about US$500, while in Switzerland there are over 40,000 hospitalizations for asthma annually, representing the largest category of direct medical expenses related to the disease.

In 2004, the Fourth Ministerial Conference on Environment and Health adopted the Children's Health and Environment Action Plan for Europe, which includes four regional priority goals to reduce the burden of environment-related diseases in children (CEHAPE). One of the goals (Regional Priority Goal, RPG III) aims to prevent and reduce respiratory diseases due to outdoor and indoor air pollution, thereby contributing to a reduction in the frequency of asthmatic attacks, and to ensure that children can live in an environment with clean air.

Allergic diseases are supposed to be caused by a complex interaction between genetic and environmental exposures. Asthmatic patients are sensitive to allergens present in indoor environments and are often hyperreactive to a number of gasses and particles.

The different types of key exposure agents of the indoor environment that may have a role in development of allergy and asthma include microbial and chemical agents.

Microbial agents – They include endotoxin of Gram negative bacteria, fungal spores and fragments, bacterial cells, spores and fragments, microbial metabolites and allergens like house dust mites, pet allergens and fungal allergens (Ahlbom et al, 1998). The evidence for a causal link between dampness and "mold" and risk of allergy and asthma is strong, but the causal links are yet to be documented. The presence of dampness increases the onset of asthma as well.

Chemicals - Chemicals that may play an important role in triggering asthma symptoms include in particular formaldehyde; aromatic and aliphatic chemical compounds, phthalates or plastic materials and indoor chemistry products resulting from ozonolysis of terpenes may also play a role, but the evidence is more limited (ECA, 2008).

Particles - ETS and Indoor ultrafine particulate matter may play an important role in triggering asthma symptoms (Strachan, 2000), as well as wood or oil smoke, soot, or exhaust.

4.1.1 Conclusions as to policy making

Asthma, allergy and airway hyperreactivity are increasing throughout.
Indoor allergen exposure is recognized as being the most important risk factor for asthma in children, in particular for sensitisation during the first years of life. The indoor environment in general can give symptoms of a non-specific nature, which is called 'sick-building syndrome'.
Different studies have shown that dwellings and schools frequently have severe indoor problems because of poor building construction and maintenance, poor cleaning and poor ventilation; in addition, high levels of VOCs, allergens and moulds (humidity) have often been found.
The following measures should be promoted and adopted:

- avoidance of environmental tobacco smoke;
- avoidance of moisture/moulds in the building;
- avoidance of allergen sources;
- adequate cleaning and maintenance, practical shaping of the interior to facilitate cleaning and maintenance;
- good control of the maintenance of heating and ventilation to ensure a satisfactory temperature and ventilation in the classroom;
- adequate periodical monitoring of the IAQ parameters;
- appropriate training of students, teachers and school staff who are responsible for management, maintenance and cleaning.

4.2 Lung cancer

In the EU lung cancer is the most common cause of death from cancer.
It is estimated that in 2006 about 20% of all cancer deaths in the EU in 2006 were due to lung cancer, that 236,000 lung cancer deaths occurred (Ferlay et al, 2007). About 375,000 new cases of lung cancer occur every year.
The majority of the case are due to active smoking, but a not negligible proportion of the disease also occurs in persons who have never smoked. Available data in the literature indicate the role of the following indoor pollutants:
Radon - Radon is considered to be the second cause of lung cancer. From the pooling of 13 residential radon epidemiological studies in 9 EU countries it has been estimated that about 9% of lung cancer deaths may be due to radon exposure in the home (Mc Laughlin and Bochicchio, 2007).
Indoor pollutants
Environmental Tobacco Smoke (ETS) - ETS has been classified as a Group 1 carcinogen by IARC. Studies conducted in the '90s have elucidated the relationship between exposure to ETS from spouse and lung cancer risk and relative risks (RR) have been provided, resulting in 1.36 for men and 1.22 for women. A recent study (Quantitative Estimation of Lung Cancer Deaths Attributable to Passive Smoking Exposure in Europe) indicated a total of 916 (54-1928) lung cancer cases due to exposure from spouse were estimated for males and 2,449 (1,424-3,357) for females. These figures correspond to an attributable proportion of 0.5% in males and 4.6% in females. The largest burden of attributable cases derive from Western and Southern Europe (Porta, 2008).
The proportion of lung cancer cases attributable to ETS is about 0.5 in males and 4.6% in females (Boffetta et al 1998; Hackshaw et al, 1997).
Combustion particles –The initial suggestion that lung cancer incidence increases due to long-term exposure, low-level exposure to PM was provided by the Harvard Six Cities study

(Dockery, 1993). These findings were confirmed in the long-term follow-up of the American Cancer Society, consisting of ~500,000 adults from metropolitan areas throughout the USA. Results indicated that each 10μg/m^3 elevation in PM2.5 was associated with approximately a 14% increase in lung cancer mortality. Evidence is emerging that long-term exposure to low concentration of PM is associated with mortality.
European studies of PM exposure and lung cancer do not show a clear association, but uncertainties remain for the measurement of exposure and latency (Gallus et al, 2008).The main problem affecting these type of studies is represented by exposure assessment and its consequent role in cancer development. The presence of a latency after exposure in the onset of cancer also represents an element to be accounted for in the study design. Further observations are hence required to corroborate the hypothesis of an increased risk of lung cancer.
As to diesel exhaust exposure, there is evidence that it may pose a risk as to lung cancer development.
Exposure to cooking oil vapours and indoor coal burning has been shown to be associated with an increased risk of lung cancer.

4.2.1 *Conclusions as to policy making*

In Europe, to reduce ETS exposure, legislative measures (smoking ban or restriction in workplaces or public places) have been adopted in most countries, but no legislative interventions can be made for home or other private indoor environments, besides information campaigns for the public on both health effects by indoor pollution and maintenance of a healthy indoor environment (to avoid smoking at home, using cleaning products that do not emit polluting substances, to ensure adequate ventilation, etc.). The public-at-large is more conscious of the negative effects of bad outdoor than indoor air quality.
As to PM, exposure threshold levels are not yet specifically stated for indoor air. The American Society of Heating, Refrigerating, and Air-conditioning Engineers (ASHRAE) has adopted, for indoor air, the outdoor limits of the US-Environmental Protection Agency - National Ambient Air Quality Standards (US-EPA-NAAQS), as concern PM_{10} (150 μg/m^3/24h). This value is higher than the corresponding limit for outdoor air quality reported by WHO (2000), that is 50 μg/m^3/24 h. There are no indoor standards for $PM_{2.5}$. WHO suggests, for outdoors, 25 μg/m^3/24 h and 10 μg/m^3/1 year respectively (WHO, 2000).
Radon: The most common residential radon reference level being used in EU countries is 200 Bq/m^3. This reference level is a recommended value and is not a mandatory regulatory level unlike an Action Level such as 400 or 500 Bq/m^3 for radon in workplaces set by some Member States in their implementation of the EU Basic Safety Standards Directive (UNSCEAR, 2000).
WHO Air Quality Guidelines for Europe also suggest that building codes should include sections to ensure that radon daughter levels do not exceed 100 Bq/m^3 EER (Equilibrium Equivalent Radon concentration) which is similar to a radon concentration of about 200 Bq/m^3.
Cost-effective measures and technology to improve indoor air quality, available guidelines and legislation on indoor air pollution in Europe, and potential action al EU and national levels are well resumed in the report of The Towards Healthy Air in Dwellings in Europe (THADE) (http://www.efanet.org/activities/publications).
Indoor risk factors are modifiable through improved ventilation, moisture control to prevent accumulation of moulds, control of the sources of pollution, e.g., tobacco smoke (avoidance of smoking indoors), combustion appliances, consumer products.
As to indoor generated particulate matter, measures include the control of the source, improvement of ventilation, better cleaning and housing hygiene and avoiding of carpets. The use of vacuum cleaners and central vacuum cleaning systems should be encouraged, along with the development of performance criteria for vacuum cleaners, the cleaning after or before the operation hours of the schools and offices should be encouraged.

Strategies for radon exposure avoidance may be divided into the following three principal categories:
(1) Identification of houses with high radon levels and the remediation of these houses.
(2) Reduction of the average indoor radon level in a country.
(3) Coupling radon reduction strategies with national strategies aimed at reducing the consumption of cigarettes.

4.3 Chronic obstructive pulmonary disease (COPD)

COPD is "a preventable and treatable disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. It also produces significant systemic consequences" (Celli, 2004).
COPD is a chronic respiratory disorder responsible for a major burden to the society worldwide. Currently, approximate estimates indicate COPD as the fifth leading cause of global morbidity. WHO predicts that COPD will become the third leading cause of death worldwide by 2020 (Annesi-Maesano et al, 2006; de Marco et al, 2007; WHO, 2004).
Variable definitions and lung function criteria for COPD have made it difficult to quantify the prevalence of the disease around the world; in addition, a large proportion of patients with COPD in the community remain undiagnosed.
A recent summary of the world literature on COPD prevalence and the European Lung White Book (ERS, 2003) reports the prevalence of clinically relevant COPD varying in Europe from 4 to 10% of the adult population.
Active smoking is the most important risk factor for COPD. It has been estimated that about 70% of COPD related mortality is attributable to cigarette smoking.
Although most COPD cases are current or former smokers, a not negligible proportion of the disease also occurs in persons who have never smoked; the prevalence of COPD in never-smoker people in studies performed in different European countries varied from 4 to 20%.
Other risk factors than smoking may play an important role in pathogenesis and development of chronic bronchitis and COPD.
In general, we found that few studies investigated the association of non-smoking related COPD with indoor air exposure. Most studies assessed the relationship between COPD and specific occupational exposure, or the health effects of ETS exposure.
ETS exposure may increase the frequency of respiratory symptoms in adults, and that these effects are estimated to be 30-60% higher in ETS exposed compared to unexposed nonsmokers. Significant relations between ETS exposure and COPD development have been found in the elderly, too, with an OR range of 1.68-5.63 (Jakkola, 2002). The results of the reviewed epidemiological studies underline the relevance of preventative policy to reduce indoor environmental risk factors for respiratory diseases. For instance, as indicated by PAR%, the elimination of home/work ETS exposure would abate the risk for COPD of about 12% (9% for chronic cough/phlegm) in Italian never smoking women (Simoni, 2007). A study performed in the USA found that, by eliminating work exposure to gas/vapors/fumes/dusts, the incidence of COPD would be reduced of 30% (WHO, 2000).
Biomass combustion was widely investigated as risk factor for COPD, in developing countries. Few studies evaluated the effects by directly measuring levels of pollutants. Information on such exposure has been more likely collected by interview with questions on the presence of known sources of indoor pollution. Through an extensive review of epidemiological studies around the world, the estimation of the risk by biomass use for COPD results in ORs of 1.8 (1.0-2.8) in males and 3.2 (2.3-4.8) in females (Smith, 2002).
Particles from outdoor pollution are also invoked as possible risk factors of COPD.

There is evidence that long-term exposure to mould/dampness is linked to higher risk for cough, phlegm, or dyspnoea, in adults (Alipour et al, 2006; de Hartog et al, 2005; Gea, 2006; Simoni et al, 2007).

4.3.1 Conclusions as to policy making

Unfortunately, studies on the relation between COPD (or other respiratory diseases) risk and directly measured concentration of indoor pollutants, are still poor. Thus, some exposure threshold levels are not yet stated for indoor air, specifically.

The American Society of Heating, Refrigerating, and Air-conditioning Engineers (ASHRAE) has adopted, for indoor air, the outdoor limits of the US-Environmental Protection Agency - National Ambient Air Quality Standards (US-EPA-NAAQS), as concern PM_{10} (150 $\mu g/m^3$/24h) , NO_2 (100 $\mu g/m^3$/1 year), and CO (35 ppm/1 h, 9 ppm/8 h).

These values are higher than corresponding limits for outdoor air quality reported by WHO (2000), that are 50 $\mu g/m^3$/24 h for PM_{10}, 40 $\mu g/m^3$/1 year for NO_2 , and 25 ppm/1 h for CO. There are no indoor standards for $PM_{2.5}$. WHO suggests, for outdoors, 25 $\mu g/m^3$/24 h and 10 $\mu g/m^3$/1 year respectively (WHO, 2000). As regards to other common indoor pollutants, such as formaldehyde or moulds, ASHRAE reports specific indoor standards (100 mg/m^3/30 min and 150 CFU/m^3 - Colony Forming Units – for formaldheyde and moulds, respectively).

Reduction of indoor air pollution requires a combination of public health policy and protective measures taken at individual levels. The actions that can be taken at political and industrial levels are the elimination of sources of pollution, when possible, and substitution of materials and equipment that are sources of pollution, with more environmental-friendly materials.

Indoor risk factors are modifiable through improved ventilation, moisture control to prevent accumulation of moulds, control of the sources of pollution, e.g., tobacco smoke (avoidance of smoking indoors), combustion appliances, consumer products.

In Europe, to reduce ETS exposure, legislative measures (smoking ban or restriction in workplaces or public places) have been adopted in most countries, but no legislative interventions can be made for home or other private indoor environments, besides information campaigns for the public on both health effects by indoor pollution and maintenance of a healthy indoor environment (to avoid smoking at home, using cleaning products that do not emit polluting substances, to ensure adequate ventilation, etc.). The public-at-large is more conscious of the negative effects of bad outdoor than indoor air quality.

4.4 Airborne respiratory infections

Microbiological contamination of indoor environment is common and can evoke infectious diseases, especially in susceptible people.

Most common route of transmission is airborne, person to person or from a source, in particular from aquatic systems like air conditioning system, evaporative condensers, humidifiers.

The infection diseases include both well-known infections like Legionnaire's disease (the incidence of Legionnaire's disease increased from 360 cases in 2000 to 765 cases in 2005), tubercolosis, flu;and new threats like Severe acute respiratory syndrome (SARS).

Legionellosis is a respiratory disease caused by bacteria Legionellae. Most frequently human disease Legionnaire's disease is caused by L. pneumophila. Case-fatality rate can be high especially among elderly and immunocompromised individuals. Legionella is an organism that resides in the environment in pools of stagnant water. Most common route of transmission is airborne. Person to person spread does not occur. The reservoirs are aquatic systems like cooling towers, evaporative condensers, humidifiers, decorative fountains etc. Outbreaks of pneumonia have been associated with contamination of water cooling towers in large buildings, with spread of the bacteria mostly through air conditioning systems. Nowadays the new threat comes from

tap water during shower or aerosolization the tap water, e.g. by spraying etc., so it could be a severe problem of hospital environment.
Chronic pulmonary **tuberculosis** caused by Mycobacterium tuberculosis is still, despite of the vaccination, severe threat. Over one-third of the world's population now has the TB bacterium in their bodies and new infections are occurring at a rate of one per second. Not everyone who is infected develops the disease and asymptomatic latent TB infection is most common. In developed countries is the prevalence low but in many of them the number of cases is slowly growing up in last years. Unfortunately the percentage of resistant chains of mycobacterium is increasing and also those of atypical tuberculosis, which are very often multiresistant, too.
The symptoms of the airborne infectious diseases can be aggravated by exposure to environmental tobacco smoke and combustion particles.

4.4.1 Conclusions as to policy making

1. To avoid overcrowded spaces if possible esp. in schools, health care facilities, etc.
Main source of infectious agents in indoor environment are people. From that point of view is difficult to regulate source, it is not possible to have any threshold limit. But indoor environment plays important role in transmission of infectious agents – ventilation, air-conditioning, water or sewage ducts can transmit several infectious agents to rather long distances. Also overcrowded spaces increase risk of transmission of the infections agents.
2. To guarantee the minimum air exchange rate in the buildings where people have to stay.
The process of person- to- person transmission could and must be regulate especially in buildings where children and young people are concentrated, also in health-care facilities. For such buildings is suitable to use the minimal air-exchange rate per person as a sort of regulation of infections agents concentration. To achieve measured air exchange is necessary to have either air condition systems or mechanical ventilation systems in all such buildings. Using natural ventilation is mostly subjective measure and don’t guarantee the minimum air exchange especially in cities.
3. To guarantee safe water & air (limits for microbiological contamination).
Also secondary source (water, dust) can play important role even in other type of infections (alimentary – e.g. water-born cholera or some viruses causing alimentary problems). This transmission is possible to regulate also during the transmission process (limits of infection agents for drinking water, air-condition systems without water stagnation, priority of cleaning procedures of air ducts especially in health care centres and facilities for children & young people). As to Legionellosis, prophylactic measures include regular cleaning and maintenance of different water systems.
4. To achieve even better quality of the environment in health care facilities (more strict limits than for the other buildings).
There are several other facultative or obligatory pathogens with low effect for healthy people who spent their time either in well-maintained indoor environment or mostly outdoors; these agents could be harm for immunocompromised people.
One can assume that if we will be able protect ourselves against these threats, probably we will be successful also in other battles against infectious disease, either those we know or any new still unknown.

4.5 Cardiovascular morbidity and mortality

Cardiovascular disease (CVD) is the leading cause of death in the industrialized world: CVD accounts for over 4.35 million deaths (49% of all death) each year in Europe and over 1.9 million deaths (42%) in the European Union (EU).
Causes of CVD include:

Secondhand smoke - Reviews summarizing the epidemiological studies about the association between ETS and increase risk for CVD concluded that the estimate risk for CVD related to ETS is about 25-30 (He et al, 1999).
Particles - Evidence is emerging that exposure to low concentration of PM is associated with cardiovascular mortality. Several studies have shown some link between outdoor PM and gases exposure and cardiovascular disease mortality and morbidity (Rich et al, 2005).
Short-term effects of PM10 exposure include an increase in the overall cardiovascular mortality. Long-term exposure to PM2.5 has been demonstrated to be independently related to cardiovascular mortality in general, and in particular to mortality for ischemic heart disease, arrhythmia, heart failure and cardiac arrest. Current evidences suggest a link between exposure to indoor PM and cardiovascular diseases onset, however more research is needed. Also there is a need to identify the role of the ultrafine fraction.
Elevations in air pollution have also been associated with increased blood pressure.
Current evidences suggest a possible link between exposure to indoor PM and cardiovascular diseases onset, however more research is needed. Also there is a need to identify the role of the ultrafine fraction.
Carbon monoxide - At CO levels typically encountered in indoor environments, health effects are most likely to occur in individuals who are physiologically stressed, either by exercise or by medical conditions that can make them more susceptible to low levels of CO. Subpopulations at increased risk of adverse effects include: individuals with cardiovascular diseases, pregnant women also with respect to fetal exposure, children, subjects with chronic obstructive pulmonary disease, individuals with reduced blood haemoglobin concentrations (Raub, 2002).
Gaseous pollutants - Epidemiological evidences of cardiovascular effects of NO_2 exposure proceeds form studies on outdoor air pollution. Moreover, it is very difficult to differentiate the effects of nitrogen dioxide from those of other pollutants in epidemiological studies.
Literature about cardiovascular effects of SO2 is poor, and it prevalently includes studies on outdoor air pollution health effects.

4.5.1 Conclusions as to policy making

PM - Exposure threshold levels are not yet specifically stated for indoor air. The American Society of Heating, Refrigerating, and Air-conditioning Engineers (ASHRAE) has adopted, for indoor air, the outdoor limits of the US-Environmental Protection Agency - National Ambient Air Quality Standards (US-EPA-NAAQS), as concern PM10 (150 μg/m3/24h). This value is higher than the corresponding limit for outdoor air quality reported by WHO (2000), that is 50 $\mu g/m^3$/24 h. There are no indoor standards for PM2.5. WHO suggests, for outdoors, 25 $\mu g/m^3$/24 h and 10 $\mu g/m^3$/1 year respectively (WHO, 2000).
ETS - The adverse effects of exposure to environmental tobacco smoking (ETS) are well established ETS exposure occurs in private households, work and public places. Several countries have enacted legislation that prohibits smoking in work and public places, but the interest towards policies to address exposure in households is more limited.
As to indoor generated particulate matter, measures include the control of the source, improvement of ventilation, better cleaning and housing hygiene and avoiding of carpets. The use of vacuum cleaners and central vacuum cleaning systems should be encouraged, along with the development of performance criteria for vacuum cleaners, the cleaning after or before the operation hours of the schools and offices should be encouraged.
Carbon monoxide - On the basis of human clinical data, to protect non smoking, middle-aged and elderly population groups with documented or latent coronary artery disease from acute ischaemic heart attacks and to protect the fetuses of non-smoking pregnant women from untoward hypoxic effects, a COHb level of 2.5% shoul not be exceeded. Not to exceed a COHb

level of 2.5% the following guideline values and period of time-weghted average exposures have been determined:

- 100 mg/m^3 (90 ppm) for 15 min
- 60 mg/m^3 (50 ppm) for 30 min
- 30 mg/m^3 (25 ppm) for 1 hour
- 10 mg/m^3 (10 ppm) for 8 hours

As to CO, the main measure to be adopted to reduce CO levels is controlling the source of exposure. Management options include: connecting each combustion equipment/appliance to chimney or vented hood, ensuring sufficient local extract ventilation in kitchens with gas stove, mandatory inspection and maintenance of indoor combustion devices, and CO alarms.
Following general recommendations are also suggested:
• Restrict tobacco smoking in all indoor spaces;
• Restrict the construction of attached garages, or isolate them from living and working spaces;
• Ensure that ventilation dilutes predictable indoor emissions below the guideline levels;
• Raise public awareness about indoor air risks.
Gaseous pollutants - As to nitrogen dioxide a 1-hour guideline of 200 μg/m^3 is proposed (WHO). As to ozone, the fisrt edistion of Air Quality Guidelines for Europe recommended a 1-hour guideline value of 150-200 μg/m^3.
As to NOx, preventives measures to be adopted include the control of the source, improvement of ventilation; the use of electrical kitchen appliances should be encouraged, while the use of unvented heating appliances should be avoided.

4.6 Odour and irritations (SBS symptoms)

Indoor air pollutants can often cause unspecific effects. A multitude of biological mechanisms are involved at the same time in the responses to multiple exposures indoors and only few objective measurements are available (Berglung et al, 1992; Chao et al, 2003; Dalton, 1999; Fanger, 2006).
The most frequent effects include acute physiological or sensory reactions, psychological reactions, and sub-acute changes in sensitivity to environmental exposures. The term Sick Building Syndrome (SBS) is used to describe cases in which building occupants experience acute symptoms and discomfort that are apparently linked to the time they spend in the building, but for which no specific illness or cause can be assigned (Fang et al, 2004).
Many different symptoms have been associated with SBS, including respiratory complaints, irritation, and fatigue.
Sensory perception of odours and mucous irritation lead to perception of poor air quality and possible risks thereof and consequently to stress or behavioural responses (opening a window, leaving the building). Other environmental stressors such as noise, vibration, crowding, ergonomic stressors and inadequate lighting can produce symptoms that are similar to those of poor air quality.
Recent studies have also shown negative effects of IAQ on office productivity and school learning (Seppanen et Fisk, 2004; Wargocki et al, 2000).
The fraction of the incidence/prevalence of reports of discomfort and symptoms which can be related to indoor air quality is not exactly known. However, in buildings without specific complaints of poor IAQ the prevalence is often close to zero and normally below 30% of the occupants. In affected buildings the prevalence often ranges between 50 and 100% of the occupants.
The relevant indoor air pollutants that can cause these effects are those which alone or in combination can stimulate our senses or cause tissue changes, and include in particular volatile organic compounds, viable or non-viable aerosols and particulate matter. The risk factors also

include technical causes such as ventilation, humidity and temperature.

4.6.1 Conclusions as to policy making

From the previous chapters it appears that indoor air pollutants cause unspecific effects and that these do not unambiguously identify the exposure. A multitude of biological mechanisms are involved at the same time in the responses to multiple exposures indoors and only few objective measurements are available. Some types of responses can not be replaced by objective measurements and often the effects and exposure cannot be quantified. Added to this, the resulting subjective reports are affected by bias and response modifiers. It follows that traditional toxicological procedures for the establishment of guidelines seem difficult to use for these subjective responses and evaluations and rational preventive actions therefore must take into account the level of toxicological knowledge available for different polluting agents and their health effects.From this it follows, that if IAQ guidelines are to be established based on subjective perceptions or symptoms reports three types of D-R relations must be considered and consequently also three types of guidelines. These are perceptions and symptoms with known causality, based on quantifiable effects and exposures, symptoms with unknown causality, and suggested or hypothetical causalities waiting for further investigations before rational decisions can be made. Because of the ill-defined causality, lack of quantifiable effects and exposure measurements etc. no strict traditional guidelines can be established. However, the importance of such complaints is well documented and guidance, recommendations, labelling systems, and emission control in these cases become the preferred tool of prevention. These less strict guidelines are acceptable only for discomfort and SBS etc. and only if possible averse health effects can be excluded e.g. because all relevant exposures are under guideline regulation as mentioned above. In any case an ALARA principle should be followed. Also the combined effects of cocktail exposures are unsolved both scientifically and administratively. Some procedures based on an assumed additivity may be taken over from occupational guideline settings. An example of the complex nature of such guidelines is Endotoxin in building dust which may indicate dampness and possible microbial growth and thus increased risk of building-related symptoms including building-related asthma, respiratory, and systemic symptoms (Park et al 2006). Building type especially open-plan offices may be a risk factor for adverse environmental perceptions and symptoms (Peitersen et al 2006). For most of the health effects for which objective measurements are available D-R relations and thresholds are not available and few of the thousands of relevant chemicals have been examined at low exposure levels. Despite this some progress has been seen. Recently several groups have discussed guideline settings for the most IAQ relevant compounds (WHO 2006, 2007, Cochet et al 2006, Kotzias et al 2005, Anonymous 2006). Several procedures for prioritizing are available by which the most important pollutants can be identified. However, no consensus exists. While we are waiting for missing data, substitute measures might be helpful. At low IAQ exposure range a lowest concentrations of interest (LCI) type of estimates may be useful. Recommended low and a higher action levels may also apply (Bluyssen et al 1997). Again no consensus exists for such procedures. Under all circumstances an ALARA principle should be followed.The preferred guidelines therefore are based on source and emission control. A typical example is formaldehyde from particle boards. Such guidelines are based on an assumed ventilation of the rooms to ensure that the exposure threshold is not exceeded. Existing ventilation guidance therefore has other functions than minimizing energy consumption.Indoor air temperature and humidity may be important for the perceived air quality and SBS symptoms (Fang et al 2004) and perceived indoor environments, non-specific symptoms, and their associations are associated with the season (Mizoue et al 2004).

REFERENCES

Anonymous, Guidance for setting occupational exposure limits: Emphasis on data-poor substances. Report no. 101. 2006. pp.1-86. ECETOX, Brussels, Belgium.

Ahlbom, A., Backman, A., Bakke, J., Foucard, T., Halken, S., Kjellman, N.I.M., Malm, L., Skerfving, S., Sundell, J. and Zetterström, O. (1998) NORDPET. Pets indoors - A risk factor for or protection against sensitisation/allergy. A Nordic interdisciplinary review of the scientific literature concerning the relationship between the exposure to pets at home, sensitization and the development of allergy. Indoor Air 8, 219-235.l

Alipour S, Deschamps F, Lesage FX. Effects of environmental tobacco smoke on respiratory symptoms and pulmonary function. Inhal Toxicol 2006;18: 569-73.

Annesi-Maesano I. Epidemiology of chronic obstructive pulmonary disease. Eur Respir Mon 2006;38: 41–70.

Beasley R. Worldwide in prevalence of symptoms of asthma, allergic rhinoconjuntivitis, and atipoc eczema: ISAAC. The Lancet, 1998, 351 (9111): 1225.

Berglund B, Brunekreef B., Knöppel H., Lindvall T., Maroni M, Mølhave L., Effects of Indoor Air Pollution on Human Health. Indoor Air 1992; 2:2-25.

Bluyssen,P.M., Cochet,C., Fischer,M., Knöppel,H., Levy,L., Lundgren,B., Maroni,M., Mølhave,L., Rothweiler,H., Saarela,K., Seifert,B., Evaluation of VOC emissions from building products, Solid flooring materials. Report 18, EUR 17334EN Ed. 1997. Pp 1-109, Eurpoean Commission, JRC, Ispra, Italy.

Boffetta P, Agudo A, Ahrens W, et al. Multicenter case-control study of exposure to environmental tabacco smoke and lung cancer in Europe. J Natl Cancer Inst 1998; 90: 1440-50.

CEHAPE Children's Environment and Health Action Plan for Europe, WHO Regional Office for Europe.

Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23: 932-46.

Chao H.J., Schwartz J., Milton D.K., Burge H.A. The work environment and workers' health in four large office buildings. Environ.Health Perspect. 2003;111: 1242-1248.

Cochet,C., Fernandes,E.O., Jantunen,M., Lindvall,T., Maroni,M., McLaughlin,J.P., Mølhave,L., Seifert,B., Strategies to determine and control the contributions of indoor air pollution to total inhalation exposure (STRATEX), EUR 22503, Report 25. 2006. pp 1-77. European Commission, Joint Research Center, Ispra, Italy.

Dalton P. Cognitive influences on health symptoms from acute chemical exposure. Health Psychol. 1999; 18: 579-590.

de Hartog, J.J., et al., Effects of fine and ultrafine particles on cardiorespiratory symptoms in elderly subjects with coronary heart disease: the ULTRA study. Am J Epidemiol, 2003. 157(7): p. 613-23.

de Marco R, Accordini S, Cerveri I, Corsico A, Anto JM, Kunzli N, Janson C, Sunyer J, Jarvis D, Chinn S, Vermeire P, Svanes C, Ackermann-Liebrich U, Gislason T, Heinrich J, Leynaert B, Neukirch F, Schouten JP, Wjst M, Burney P. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. Am J Respir Crit Care Med 2007;175: 32-9.

Dockery, D.W., et al., An association between air pollution and mortality in six U.S. cities. N Engl J Med, 1993. **329**(24): p. 1753-9.

ECA Report No. 2, Formaldehyde emission from wood-based materials: guideline for the determination of steady state concentrations in test chambers. EUR 12196 EN, 1989.

ECA Report No. 6, Strategy for sampling chemical substances in indoor air. EUR 12617 EN, 1989.

ECA Report No. 7, Indoor air pollution by formaldehyde in European countries. EUR 13216 EN, 1990.

ECA Report No. 8, Guideline for the characterization of volatile organic compounds emitted from indoor materials and products using small test chambers. EUR 13593 EN, 1991.

ECA Report No. 11, Guidelines for ventilation requirements in buildings. EUR 14449 1992, EN.

ECA Report No. 12, Biological particles in indoor environments. EUR 14988 EN, 1993.

ECA Report No. 14, Sampling strategies for volatile organic compounds (VOCs) in indoor air. EUR 16051 EN, 1994.

ECA Report No. 15, Radon in indoor air., EUR 16123 EN, 1995.

ECA Report No. 16, Determination of VOCs emitted from indoor materials and products: Second interlaboratory comparison of small chamber measurements., EUR 16284 EN, 1995.

ECA Report No. 17, Indoor air quality and the use of energy in buildings. EUR 16367 EN, 1996.

ECA Report No. 18, Evaluation of VOC emissions from building products –solid flooring materials., EUR 17334 EN, 1997.

ECA Report No. 22, Risk assessment in relation to indoor air quality, EUR 19529/EN, 2000.

Edwards RD, Schweizer C, Jantunen M, Lai HK, Bayer-Oglesby L, Katsouyanni K, Nieuwenhuijsen M, Saarela K, Sram R, Künzli N (2005) Personal exposures to VOC in the upper end of the distribution — relationships to indoor, outdoor and workplace concentrations. Atmos Environ, 39(12):2299-2307.

Engdahl F. Evaluation of Swedish ventilation systems. Building and Environment. 33:4: 197-200.

ERS, European Respiratory Society. European Lung White Book: Huddersfield, European Respiratory Society Journals, Ltd; 2003.

Fang L., Wyon D.P., Clausen G., Fanger P.O. Impact of indoor air temperature and humidity in an office on perceived air quality, SBS symptoms and performance. Indoor Air 2004;14 Suppl 7: 74-81.

Fanger, O.P., What is IAQ? Indoor Air 2006;16: 328-334.

Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007; 18: 581-592.

Franchi M, Carrer P, Kotzias D, Rameckers EM, Seppanen O, van Bronswijk JE, Viegi G, Gilder J A, Valovirta E. Working towards healthy air in dwellings in Europe. Allergy 2006, 61(7):864-868.

Gallus S, Negri E, Boffetta P, McLaughlin JK, Bosetti C, La Vecchia C. European studies on long-term exposure to ambient particulate matter and lung cancer. Eur J Cancer Prev. 2008 Jun;17(3):191-4.

G.U. Gazzetta Ufficiale n. 276, 27/11/2001Gea J. Wood smoke exposure and risk of chronic obstructive pulmonary disease. Eur Respir J 2006;27: 542-6.

Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. BMJ 1997; 315: 980-988.

He J, Vupputuri S, Allen K, Prerost MR, Hughes J, Whelton P. Passive smoking and the risk of coronary heart disease – A meta-analysis of epidemiologic studies. N Engl J Med 1999;340: 920-6.

Jaakkola MS. Environmental tobacco smoke and health in the elderly. Eur Respir J 2002;19: 172-81.

Jantunen MJ, Hänninen O, Katsouyanni K, Knöppel H, Künzli N, Lebret E, Maroni M, Saarela K, Srám R, Zmirou D Air pollution exposure in European cities: the EXPOLIS-study. J Exposure Anal Environ Epidemiol, 1998: 8(4): 495-518.

Kotzias D, Koistinen K, Kephalopoulos S, Schlitt C, Carrer P, Maroni M, Jantunen M, Cochet C, Kirchner S, Lindvall T, McLaughlin J, Mølhave L, de Oliveira Fernandes E and Seifert B. Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU. The INDEX project: Final Report. EUR 21590 EN. EC DG JRC. Institute for Health and Consumer Protection. Physical and Chemical Exposure Unit. 2005. 331 pp.

McLaughlin and Bochicchio. First EnVIE conference, Helsinki 2007.

Mendell M, Fisk WJ, Kreiss K, Levin H, Alexander D, Cain WS, Girman JR, Hines CJ, Jensen PA, Milton DK, Rexroat LP, Wallingford KM. Improving the Health of Workers in Indoor Environments: Priority Research Needs for a National Occupational Research Agenda. American Journal of Public Health, 2002, 92:9.

Mizoue T., Andersson K., Reijula K., Fedeli C. Seasonal variation in perceived indoor environment and nonspecific symptoms in a temperate climate. J.Occup.Health 2004; 46: 303-309.

Porta D, Forastiere F, Perucci C. First EnVIE Conference, Helsinki.

Raub J.A. and Benignus V.A. Review: Carbon monoxide and the nervous system. Neuroscience and Biobehavioral Reviews 2002; 26: 925–940.

SCHER (Scientific Committee on Health and Environmental Risks). Opinion on risk assessment on indoor air quality. European Commission 2007.

Seppänen, O.A., Fisk,W.J., Summary of human responses to ventilation. Indoor Air 2004. 14 Suppl 7, 102-118.

Simoni M, Baldacci S, Puntoni R, Pistelli F, Farchi S, Lo Presti E, Pistelli R, Corbo G, Agabiti N, Basso S, Matteelli G, Di Pede F, Carrozzi L, Forastiere F, Viegi G. Respiratory symptoms/diseases and environmental tobacco smoke (ETS) in never smoker Italian women. Respir Med 2007;101: 531–538.

Smith KR, Mehta S, Feuz M. The global burden of disease from indoor air pollution: results from comparative risk assessment. Proceedings of Indoor Air 2002;IV:10-19.

Strachan, D.P. (2000) The role of environmental factors in asthma. Br Med Bull 56, 865-82.

THADE report. Franchi M, Carrer P, Kotzias D, Rameckers EMAL, Seppänen O, van Bronswijk JEMH, Viegi G. Towards Healthy Air in Dwellings in Europe. Naples, Italy 2004.

UNSCEAR, 2000 United Nations Scientific Committee on the Effects of Atomic Radiation.

Wargocki P, Bako-Biro Z, Clausen G, et al. Air quality in a simulated office environment as a result of reducing pollution sources and increasing ventilation. Energy and Buildings. 34:8: 775-783.

WHO, 2000: Air Quality Guidelines for Europe. WHO Regional Publications, European Series, No. 91, Regional Office for Europe, Copenhagen.

WHO, 2004. The World Health Report 2004: changing history. World Health Organization, Geneva, Switzerland.

WHO, 2005. Air Quality guidelines-Global update.

WHO, 2006: Air Quality Guidelines – Global Update 2005. World Health Organisation, Regional Office for Europe, Copenhagen. 484 pp.

WHO. Development of WHO Guidelines for indoor air quality, Report of a working group meeting, Bonn, Germany 23-24 October, 2006. EOR/05/5067585 Ed. WHO regional office for Europe, Copenhagen, Denmark. 2006.

ANNEXES

Allergic and asthma symptoms

Jan Sundell1, Barbara Kolarik1,2, Kiril Naydenov1, Malin Larsson4, Linda Hagerhed-Engman3 Carl-Gustaf Bornehag1,3,4

1 Technical University of Denmark, Dept. of Mechanical Engineering, International Centre for Indoor Environment and Energy, DK-2800 Lyngby, Denmark;
2 Silesian University of Technology, Faculty of Environmental Engineering and Energy, Konarskiego 18, 44-101 Gliwice, Poland
3Department of Building Physics, Swedish National Testing and Research Institute, Box 857, S- 501 15, Boras, Sweden
4Public Health Sciences, Karlstad University, Universitetsgatan 2, S-651 88, Karlstad, Sweden

Background

The incidence of asthma and allergy has increased throughout the developed world over the past forty years (Beasley, 2003). The incidence is much higher for children than adults. From being a relatively uncommon disease, a few decades ago, allergies today, in many regions, are affecting a large part of the population. The European Allergy White Paper (1997) noted that with the exception of AIDS, only few diseases, besides allergies, have increased two- or three-fold within a short time. Allergic diseases are supposed to be caused by a complex interaction between genetic and environmental exposures. The temporal trends in allergy prevalences, the differences in the risk of allergy between urban and rural populations of the same ethnicity and the short time period for which the prevalence of allergic diseases have increased, indicate that changes in environmental exposures rather than genetic factors are the most likely explanation for the increase (Etzel, 2003; Strachan, 2000).

The Global Burden of Asthma Report, indicates that nearly 30 million people currently have asthma in Scandinavia, the Baltic States, the UK, Republic of Ireland, and Western Europe; throughout Europe, the prevalence of asthma is generally higher in urban areas compared with suburban and rural areas, the incidence of asthma attacks diagnosed by general practitioners in the UK and Republic of Ireland is about 5 times higher than it was 25 years ago; the recent increase in asthma prevalence has been particularly marked in the former East Germany, which now has prevalence rates similar to those in former West Germany; similar increases are expected to occur in the former socialist countries of the Baltic region in coming years, as these communities increasingly adopt Western lifestyles.

In western Europe, the symptom rate is up to ten times that in eastern countries. For 1995-1996, the International Study of Asthma and Allergies in Childhood (ISAAC) found an 11.5% annual average prevalence of self-reported asthma symptoms in children aged 13–14 years Europe-wide.

Globally, the prevalence of asthma and allergies has increased over the last few decades. However, the ISAAC study, which focused on children, showed wide variations in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis and eczema. In general, the study found the highest asthma prevalence in English-speaking developed countries (Australia, Ireland, New Zealand, the United Kingdom and the United States). The rate ranges from 2.6–4.4% in Albania, Romania, Georgia, Greece and the Russian Federation to 29.1–32.2% in Ireland and the United Kingdom. This suggests that a western lifestyle is associated with allergic diseases in childhood. Among children aged 13–14 years, the greatest increases in prevalence between ISAAC Phase One (1992–1998) and Phase Three (1999–2004) were found in Romania and

Ukraine for asthma, and Poland, Romania and the Russia Federation for rhinoconjunctivitis. The prevalence of asthma and rhinoconjunctivitis fell in Ireland, Malta and the United Kingdom (Beasley, 2003).

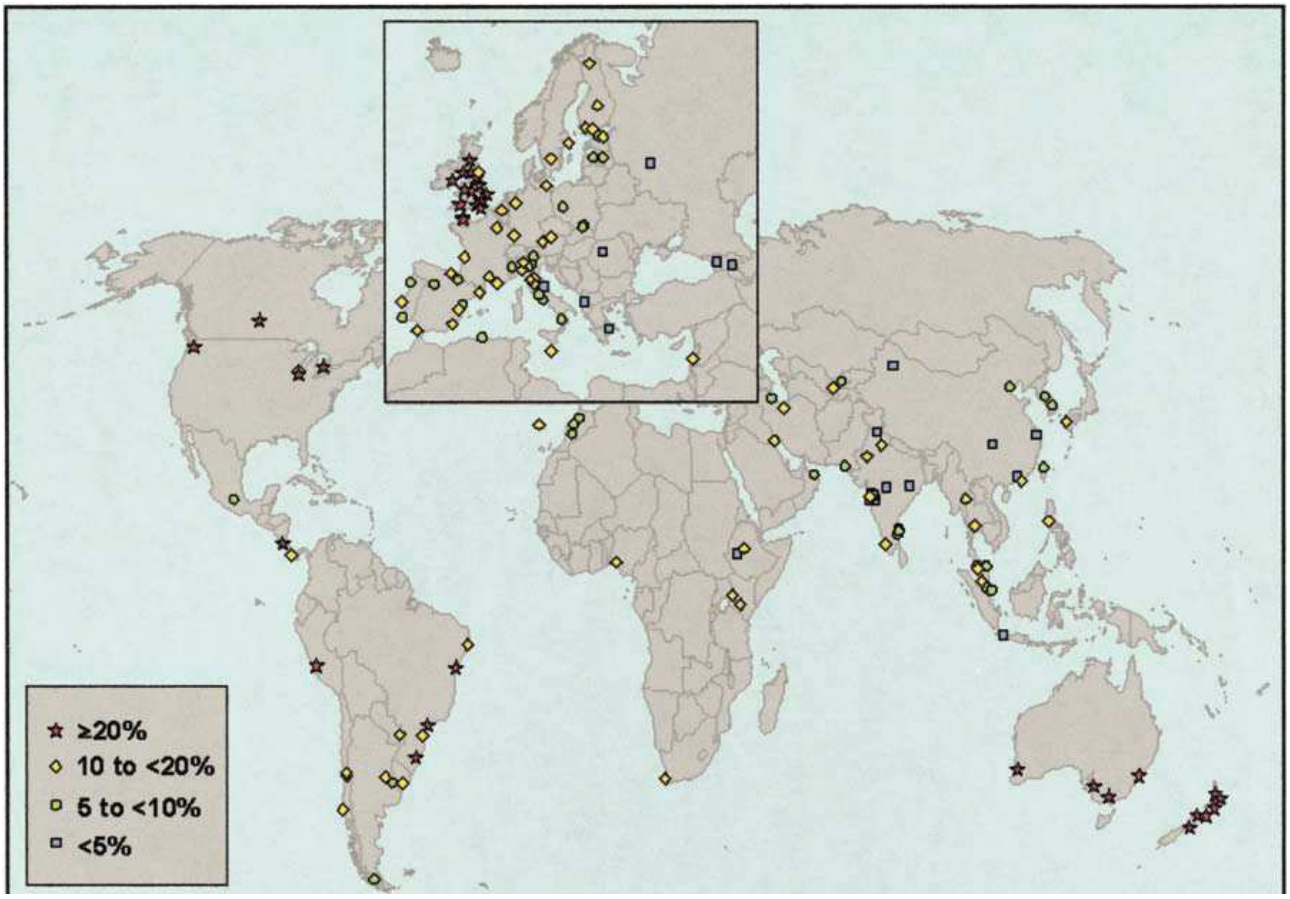


Fig. 1. ISAAC map of asthma symptom prevalence (From Asher MI, Anderson HR, Stewart AW, et al.
Worldwide variations in the prevalence of asthma symptoms: International Study of Asthma and Allergies in Childhood (ISAAC). Eur Respir J 1998;12:315– 35

But, what changes in environmental exposures are important for the increase in allergies?
In the search of causative factors it's important to note that small children are particularly at risk. Thus the exposure during pregnancy and first years of life seems more important than exposure later in life. Children have a higher metabolism and faster respiratory rate compared to adults resulting in higher intake of food, drink and air per unit of body volume, i.e. higher dose which is further enforced by their hand-to-mouth behavior. The exposure (in mass) during pregnancy is defined by the exposure of the mother, while the exposure of babies mainly consist of indoor air (around 80%), and food, mainly breastmilk. In developed countries more than 50 % of the total exposure (in mass), during a 70 year life consists of air in the home, while outdoor air, food and liquids, and industrial air stands for around 7% each. The rest of the exposure is air in schools, day care, offices, and during traveling.
This review is based on multidisciplinary state-of-art reviews of the scientific literature on associations between indoor exposures and asthma and allergies (Ahlbom, 1998; Andersson, 1997; Bornehag, 2001; 2004; Wargocki, 2002), and on results from two ongoing studies in Sweden and Bulgaria, DBH, and ALLHOME. The studies in Sweden and Bulgaria are basically identical, starting with a cross-sectional questionnaire study on small children, allergic

manifestations and home environmental factors. The second step has been nested case-control studies including clinical examinations, inspections and environmental measurements.

Causes of the increase in asthma/allergies

Even if genetic changes is not the cause of the increase, genetic predisposition is an important factor for the risk of getting asthma and allergies. In a questionnaire study of 1,325 children, 7 years of age, Kjellman (1977) observed the highest prevalence of atopic disease among children of parents with an identical type of atopic disease (with 72% risk), and the lowest among children of parents without an atopic disease (10% risk). Small boys have a higher prevalence of atopic diseases than small girls, but this changes during puberty.

As allergy means that a person reacts to an allergen (e.g. from cat, dog, pollen, mite, mould, cockroaches, specific food etc), the most simple explanation for the increase should be that we are exposed to more allergens today. Even if there are indications of increased allergen levels from mites and moulds (due to tighter, less ventilated, and thus more humid, buildings in northern climate), and, perhaps more pet contacts, there is no scientific data showing that this is an important factor behind the increase in allergies, worldwide.

If the allergen levels can not explain the increase, there must be other environmental changes that are the cause. Either our immune defence is changed (due to e.g. lack of microbial exposure), so that we react to harmless proteins, allergens, more than before (the hygiene hypothesis), or some other exposure (adjuvant factors) makes us more vulnerable (mechanisms not known) for exposure to allergens.

The hygiene hypothesis involving factors like family size and number of early infections is, by far, the most popular, discussed and studied explanation for the rising trends in allergy and asthma (Platt Mills, 2005). It suggests that exposure to infections early in life influences the development of a child's immune system along a "non allergic" pathway, leading to a reduced risk of asthma and other allergic diseases. However, despite numerous studies, (including up to 100 published state-of-the-art reviews), the area is controversial. E.g. the hypothesis does not fit for USA, where the allergy prevalence is very high among children in inner cities such as Harlem, where an increased hygiene is most certainly not a problem. The summary of the state-of-the art reviews is that there is very little, if any, consistent evidence for this hypothesis.

If changed hygiene can not explain the increased morbidity, what about new environmental exposures?

Some outdoor exposures, such as ozone, nitrogen dioxide, sulphur oxides and particulate matter are known to exacerbate asthma (Burnett, 2001; Dockery, 1989; Ware, 1986; Shima, 2000). In Bulgaria, Lubomirova et al. (2000) reported a higher prevalence of respiratory and allergic diseases among children exposed to air pollution (organic solvents) from refinery and petrochemical plant compared to control children. Outdoor air also constitutes a main source of exposure to air-borne allergens, such as pollen from plants and moulds. The European Community Respiratory Health Survey reported that mold exposure in the last year was associated with asthma symptoms and bronchial responsiveness (OR range, 1.14-1.44) (Zock JP, 2002).

Mold spore counts for Cladosporium and Aspergillus were associated with an increased risk of allergic sensitization. Sensitized children exposed to high levels of mold spores (> 90th percentile) were more likely to suffer from symptoms of rhinoconjunctivitis. Elevated indoor concentrations of molds in wintertime might play a role in increasing the risk of developing atopic symptoms and allergic sensitization not only to molds but also to other common, inhaled allergens (Jacob, 2002)

However the role of outdoor air pollution in causing asthma remains controversial (ATS, 2000). E.g. the prevalence of allergic sensation was three times higher in low polluted Sundsvall (Sweden) than in Konin (Poland), where the levels of common industrial pollutants, SO2 and smoke particles were much higher (Braback, 1995). In a review of the evidence regarding the link between environmental exposures and the prevalence of asthma, Etzel (2003) concluded that outdoor air exposures are not likely to cause the increase in asthma prevalence.

Diet (Vevereux, 2006), lack of breastfeeding (van Odijk, 2003), less physical activity and obesity (Shore, 2006). are factors discussed as possible causes behind the increase in asthma/allergies. It is shown that breast-feeding has a protective effect. Otherwise there is no good scientific data behind these ideas.

Indoor air

The air indoor comes from the air outdoor. Outdoor air contain pollutants that are present due to e.g. traffic, soil, vegetation (pollens) and industries (Bates, 1995). Inside the room, the air receives further contaminations from people, animals, furniture, furnishings and building materials, cooking, vacuum cleaning, combustion processes and smoking as well as from cleaning products, microbial growth, etc.

Exposure to secondhand smoke can cause new cases of asthma in children who have not previously shown symptoms. Exposure to secondhand smoke can trigger asthma attacks and make asthma symptoms more severe. For household ETS exposure, a consistent effect was seen only at ≥20 cigarettes smoked per day. Adjusted odds ratios for increased risk (95% confidence interval) for household exposures (≥20 cigarettes smoked per day vs none smoked) and maternal prenatal exposure (prenatal smoking vs no smoking), respectively, for children 2 months to 2 years old were three or more episodes of wheezing, 2.7 (1.7, 4.2), 2.1 (1.5, 2.9); and for children 2 months to 5 years old were asthma, 2.1 (1.4, 3.2); 1.8 (1.3, 2.6) (Gergen, 1998) An Italian study DRIAS (Disturbi Respiratori nell'Infanzia e Ambiente in Sardegna: Respiratory Symptoms in children and the Environment in Sardinia, Italy) found thar exposure to ETS and family atopy have a joint effect resulting in an almost tripling of prevalence for current wheeze and more than four times for current asthma. Maternal smoking during pregnancy and/or in the first year of life remained associated with wheeze in the first year of life (odds ratio, 1.88; 95% confidence interval, 1.14–3.12; P¼0.01). ETS exposure in ‘‘high-risk’’ infants increases the risk of wheezing starting in the first year of life, but not after age 1 year (Le Souef, 2004). A population-based study of > 4,000 school-aged children indicated that asthma diagnosis before 5 years of age was associated with exposures in the first year of life to wood or oil smoke, soot, or exhaust (OR = 1.74; 95% CI, 1.02–2.96), cockroaches (OR = 2.03; 95% CI, 1.03–4.02), herbicides (OR = 4.58; 95% CI, 1.36–15.43), pesticides (OR = 2.39; 95% CI, 1.17–4.89), and farm crops, farm dust, or farm animals (Salam, 2004). A remarkably consistent association between home dampness and respiratory symptoms and asthma has been observed in a large number of studies conducted across many geographic regions. In a recent review of 61 studies, it was concluded that dampness was a significant risk factor for airway effects such as cough, wheeze, and asthma, with odds ratios ranging from 1.4 to 2.2. Positive associations have been shown in infants, children, and adults, and some evidence for dose-response relations has also been demonstrated (Douwes, 2003). In two multidisciplinary reviews on moisture related problems in buildings (dampness) and associated health effects it was concluded that “dampness” do increase the risk for several health effects such as asthma and allergies, sick building syndrome and airway infections (Bornehag, 2004; Wargocki, 2002). Identified health relevant moisture problems were e.g. visible mould and damp spots, detached or miss-colored flooring materials, condensation on inside of window panes, flooding and bad odor. However, the literature did not show what dampness related exposures that were responsible for the health

effects. The results from the DBH and ALLHOME studies are well in line with earlier major studies on dampness and health. In both studies strong and consistent associations were found between moisture related problems indoor and symptoms among children. The risk for symptoms was more than doubled for children living in a home with self reported “dampness” (Bornehag, 2004; Naydenov, 2005). In Sweden visible mould or damp spots were reported from the index child bedroom in 1.4% of homes compared to 35% in Bulgaria. In general no associations was found in Sweden between health effects and type of mould, a mouldy odour in the room, glucan, ergosterol, and mVOC. However an association between symptoms and Penicillium in dust, and a strong dose-response relationship between rhinitis and eczema and inspectors perceptions of a mouldy odour along the skirting board (Hagerhe-Engman, 2006). Results from Bulgaria are pending analyses.The Nordic interdisciplinary review, NORDPET (Ahlbom, 1998), concluded that pet exposure in infancy increases the risk for sensitization (OR 1.0-1.5). Pet keeping as a risk factor for asthma and wheezing in children was also reported in the review by Apelberg et al. (2001). However, in a study by Lau et al. (2000) no relation was found between early indoor pet allergen exposure and prevalence of asthma, wheeze, and bronchial hyper-responsiveness. In a number of studies (Holscher, 2002; Nafstad, 2001) an inverse relationship between early pet exposure and allergic diseases later in life has been found, suggesting a “protective” effect of pet keeping. Such inverse associations between current or early life pet ownership and symptoms are, however, mainly due to avoidance behaviour in the families,(Bornehag, 2003), i.e. a “healthy pet keeping” effect. In Sweden where a number of information campaigns to the general public, about risk factors for asthma and allergies, there is a strong “protective effect” of pet exposure, while in Bulgaria with no such campaigns, there is no “protection” from pet keeping. Meaning, in countries with a good knowledge about the risk for allergies related with pets, families with allergies tend to get rid of pets, while that is not the case in countries without such public knowledge.

A study indicated that children sensitized at least once during the first 3 years of life were found to be exposed to significantly higher house dust mite (median, 868 ng/gm vs 210 ng/gm; p = 0.001) and cat (median, 150 ng/gm vs 64 ng/gm; p = 0.011) allergen concentrations in domestic carpet dust compared with the group without sensitization. In homes with low (<= 25th percentile) dust concentrations, the risk of sensitization to mite (1.6%) and cat (2.0%) is low, compared with 6.5% for mite and 6.3% for cat if the domestic exposure is above the 75th percentile (Wahn U. 1997).
Reduced ventilation rates means increased concentrations of building related pollutants, including moisture. Only few studies on the association between health effects and ventilation rates in homes have been reported. Oie et al. (1997) found that the risk of bronchial obstruction not directly was associated with the ventilation rate in the homes, but that the risk associated with e.g. dampness was greatly increased in homes with a low ventilation rate. Emenius et al. (2004) reported that air change rate and type of ventilation system did not affect the risk of recurrent wheezing. However, in a study by Bornehag et al. (2004) case children had significantly lower ventilation rates at home than controls and a dose-response relationship was indicated. An important difference between these studies are that the ventilation rate in the study by Emenius et al. are reported to be about the double of that in the study by Bornehag et al.

The literature on HDM (Harving, 1993; Sundell, 1995) indicates that inadequate ventilation in homes in cold climate constitute a major risk factor for infestation of mites and subsequent health effects.

It is well established that ventilation rates in homes in northern Europe have been reduced during the last decades, as a result of energy conservation measures. About 60% of the multi-family houses and about 80% of the single-family houses in Sweden (Sundell, 1995) .

Indoor smoke from solid fuels (Desai, 2004) and environmental tobacco smoke (Tatum, 2005) are significant triggers for asthma symptoms and attacks. The situation with regard to smoking is totally different between Sweden and Bulgaria. In Sweden smoking among pregnant women is rare, and "no one" smokes in a room with a baby, while in Bulgaria 31% of the pregnant women were smoking, and 73% of the children had at least one family member smoking. Smoking is a risk factor for asthma in both countries, but much more pronounced in Bulgaria. Especially a mother smoking during pregnancy, and first year of life of the child were significantly associated with most of the health effects among the children. Adverse effects of both pre- and postnatal parental smoking on children's respiratory health were recently confirmed by Pattenden et al. (2006). Asthma was most strongly associated with maternal smoking during pregnancy, but postnatal exposure showed independent associations with a range of other respiratory symptoms.

Chemical exposures indoors

The home environment has changed considerably during the past 3-5 decades because of the introduction of new building technology, as well as new building materials. Some new surface materials are emitters of chemical compounds with potential allergic properties.

Commonly measured VOCs have not been strongly and consistently associated with asthma/allergies. There is, however, some epidemiological evidence for associations between phthalates or plasticized products such as PVC and allergic symptoms in the airways (e.g. asthma), nose and skin. Jaakola et al. (1999) found that the total area of PVC surface materials in homes was associated with development of bronchial obstruction in small children in Norway (Jaakola, 2000). In another study from Finland lower respiratory tract symptoms, like persistent wheezing, cough and phlegm in children, were associated with the presence of plastic wall materials, while upper respiratory tract symptoms were not. Also the relative risk estimated for pneumonia, bronchitis and otitis media were slightly increased in the presence of plastic wall materials (Nielsen). In the first phase of the Swedish DBH-study it was found that PVC as flooring material in combination with moisture problems in the floors was associated with e.g. asthma among children aged 1-6 years (Glue, 2005), the same is valid for Bulgaria. Furthermore, in the second phase of the DBH-study a strong dose-response relationship was found between asthma and di(2-ethyl-hexyl)-phthalate (DEHP) concentration in indoor dust and between eczema and rhinitis and butyl-benzyl-phthalate (BBzP) (Bornehag, 2004). Oie et al. (1997) elaborated possible mechanisms of respiratory effects by inhalation exposure and concluded that deposition of DEHP in the lungs may increase the risk of inflammation in the airways which is a characteristic feature of asthma. In a population-based incident case-control study among adults (21-63 years), Jaakkola et al (2006) reported that the use of self leveling compounds at home during the past 12 months was a determinant of onset of asthma. They also found that the risk of asthma was significantly related to the presence of plastic wall materials at work. Reviewing existing literature, Nielsen et al (2006) supported the hypothesis that some phthalates may act as adjuvants. An adjuvant effect of phthalates for sensitization to common allergens was tested by Glue et al. (2005). None of the phthalates tested was found to induce histamine release per se, however, higher histamine release was observed when the cells first were treated with phthalates and then exposed for allergen. Lee et al. (2004) reported that DEHP and DINP (di-isononyl phthalate) enhance allergic responses by enhancement of IL-4 production in CD4+ T cells via stimulation of NF-AT-binding activity which is in line with the discussion in the paper by Chalubinski et al. (2006).

The sources of phthalate esters indoor are ubiquitous plasticized polyvinyl chloride (PVC) materials (floor and wall covering materials), shower curtains, adhesives, synthetic leather, toys, cosmetics and very many other consumer products.

Discussion and conclusions

The increase in asthma/allergies have been dramatic all over the world, in a short time period (decades). The causes must be environmental, as the time period is to short for major genetic changes. An easy explanation would be that there have been a major increase in exposure to allergens. We are still becoming sensitized to birch, cat, dog, mites etc, and there are no scientific evidence that such sources have increased drastically the last decades. So the cause should be searched for in the way we are reacting more often to pollens, cat dander, mites today.
The most common explanation is the "hygiene hypothesis". Our environment is too clean, we are not exposed to "dirt", including microbes, that occupies the immune defense. Instead the immune system react to harmless proteins, allergens, inducing asthma/allergies. In spite of two decades of research on this hypothesis, no consistent positive confirmation have been found, rather the contrary. Probably many of the findings can be explained by selection bias. In families that have a member that gets sick when exposed it is natural to avoid pets, resulting in a seemingly "protective" effect of pet-keeping in cross-sectional or cohort studies ("the healthy pet keeping effect"). This effect is obvious in a country like Sweden, with a number of national campaigns, informing everyone about risk factors for allergies (including pets), but not existing in Bulgaria (no campaigns, pets is a real risk factor!). The same selection bias could be found among farmers, and other groups that are used as evidence of the "hygiene hypothesis". In the same field of research we have the protective effect of endotoxin. As endotoxin is strongly associated with pet keeping, we have the same strong selection bias involved. The idea that it is cleaner today (more hygienic) in homes, schools than 50 years ago, is also against common experience. From a "housewife", at home, cleaning.., we have a society were most are working outside the home. It is reasonable to assume that homes are more dirty today. For schools, day care centers, offices the development has been the same. There is in most buildings less cleaning today than was usual decades ago, as cleaning is a major cost for building owners (much more important than energy use). More frequent early infections should prevent asthma/allergies, according to the "hygiene hypothesis", but in the Swedish study (DBH), it's the opposite! The more early infections (day care attendance), the more asthma/allergies.

Indoor allergen exposure is recognized as being the most important risk factor for asthma in children, in particular for sensitisation during the first years of life. The indoor environment in general can give symptoms of a non-specific nature, which is called 'sick-building syndrome'.
Different studies have shown that dwellings and schools frequently have severe indoor problems because of poor building construction and maintenance, poor cleaning and poor ventilation; in addition, high levels of VOCs, allergens and moulds (humidity) have often been found.

Future research is also needed to clearly identify risk factors contributing to asthma and allergic disease onset. In particular the role of exposure to chemicals, such as phthalates, should receive attention.

References

Ahlbom, A., Backman, A., Bakke, J., Foucard, T., Halken, S., Kjellman, N.I.M., Malm, L., Skerfving, S., Sundell, J. and Zetterström, O. (1998) NORDPET. Pets indoors - A risk factor for or protection against sensitisation/allergy. A Nordic interdisciplinary review of the scientific literature concerning the relationship between the exposure to pets at home, sensitization and the development of allergy. Indoor Air 8, 219-235.l

American Thoracic Society (2000). What constitutes an adverse health effect of air pollution? Official statement of the American Thoracic Society. Am J Respir Crit Care Med. 161(2 Pt1):665-673.

Andersson, K., Bakke, J.V., Bjorseth, O., Bornehag, C.G., Clausen, G., Hongslo, J.K., Kjellman, M., Kjargaard, S., Levy, F., Mohave, L., Skerfving, S. and Sundell, J. (1997) TVOC and health in non-indutrial indoor environments. Report from a Nordic scientific consensus meeting at Langholmen in Stockholm. Indoor Air 7, 78-91.

Apelberg, B.,J., Aoki, Y., Jaakola, J. (2001). Systematic review; Exposure to pets and risk of asthma and asthma-like symptoms. J Allergy Clin Immunol 107(3):455-60.

Bates, D.,V. (1995). The effects of air pollution on children. Environ Health Perspect. 103:49-53

Beasley, R., Ellwood, P. and Asher, I. (2003) International patterns of the prevalence of pediatric asthma the ISAAC program. Pediatr Clin North Am 50, 539-53.

Bornehag C-G, Blomquist, G, Gyntelberg, F, Järvholm, B, Malmber, P, Nordvall, L, Nielsen, A, Pershagen, G, Sundell, J (2001). Dampness in Buildings and Health Nordic Interdisciplinary Review of the Scientific Evidence on Associations between Exposure to ‘‘Dampness’’ in Buildings and Health Effects (NORDDAMP), Indoor Air, 11, 72–86.

Bornehag C-G., Sundell, J., Bonini, S. Custovic, A., Malmberg, P., Skerfving, S., Sigsgaard, T., Verhoeff, A., (2004). Damness in buildings as a risk factor for health effects, EUROEXPO, a multidisciplinary review of the literature (1998-2000) on dampness and mite exposure in buildings and health effects. Indoor Air, 14:243-257.

Bornehag, C-G, Sundell, J, Sigsgaard, T (2004). Dampness in buildings and health (DBH), Report from an ongoing epidemiological investigation on the association between indoor environmental factors and health effects among children in Sweden, Indoor Air, 14 (Suppl 7), 59–66.

Bornehag, C-G, Sundell, J, Sigsgaard, T (2004). Dampness in buildings and health (DBH), Report from an ongoing epidemiological investigation on the association between indoor environmental factors and health effects among children in Sweden, Indoor Air, 14 (Suppl 7), 59–66

Bornehag, C-G., Sundell, J., Weschler, C.,J., Sigsgaard, T., Lundgren, B., Hasselgren, M., Hagerhed-Engman, L. (2004). The association between asthma and allergic symptoms in children and phthalates in house dust: a nested case-control study. Environ Health Perspect 112(14):1393-7.

Bornehag, C-G., Sundell, J., Hagerhed, L., Janson, S. and the DBH-study group. (2003). Pet-keeping in early childhood and airway, nose and skin syptoms later in life. Allergy 58:939-944.

Bornehag, C-G., Sundell, J., Sigsgaard, T. (2004). Dampness in buildings and health (DBH): Report from an ongoing epidemiological investigation on the association between indoor environmental factors and health effects among children in Sweden. Indoor Air ,14, Suppl 7:59-66.

Braback, L., Breborowicz, A., Julge, K., Knutsson, A., Riikjarv, M.,A., Vasar, M., Bjorksten, B. (1995). Atopic sensitizationand respiratory symptoms among Polish and Swedish school children. Clin Exp Allergy. 24(9):826-35.

Brunekreef, B., Groot, B., Hoek, G. (1992). Pets, allergy and respiratory symptoms inj children. Int J Epidemiol 21:338-342.

Burnett, R.,T., Smith-Doiron, M., Raizenne, M.,E., Stieb, D. (2001). Association between ozone and hospitalization for acute respiratory diseases in children less than 2 years of age. Am J Epidemiol. 153:444-452.

Chalubinski M. and Kowalski M.L.(2006) Endocrine disrupters – potential modulators of the immune system and allergic response. Allergy 61: 326-1335.

Desai, M.,A., Mehta, S., Smith, K.,R. (2004). Indoor smoke from solid fuels: Assessing the environmental burden of disease at national and local levels. World Health Organization, Geneva. Environmental Burden of Disease Series, No 4.

Dockery, D., W., Speitzer, F.,E., Stram, D.,O., Ware, J.,H., Spengler, J.,D., Ferris, B.,G. Jr. (1989). Effects of inhalable particles on respiratory health of children. Am Rev Respir Dis. 139(3):587-94.

Douwes J, Pearce N (2003). Invited Commentary: Is Indoor Mold Exposure a Risk Factor for Asthma? Am J Epidemiol;158:203–206

Emenius, G., Svartengren, M., Korsgaard, J., Nordvall, L., Pershagen, G., Wickman, M. (2004). Building characteristics, indoor air quality and recurrent wheezing in very young children (BAMSE). Indoor Air 14(1):34-42.

Environ Health Perspect 110:647–653 (2002).

Environ Res. 2008 Oct 24. (Epub ahead of print).

Etzel, R.A. (2003) How environmental exposures influence the development and exacerbation of asthma. Pediatrics 112, 233-9.

European Allergy White Paper (1997). The UCB Institute of Allergy.

Gergen PJ, Fowler JA, Maurer KR, Davis WW, Overpeck MD 1998, PEDIATRICS, 101,2,8 February.

Glue Ch., Platzer M.H., Larsen S.T., Nielsen G.D., Skov P.S., Poulsen L.K. Phthalates potentiate the response of allergic effector cells. Basic & Clinical Pharmacology & Toxicology (2005) 96: 140-142.

Hagerhed-Engman, L. (2006). Indoor environmental factors and its associations with asthma and allergy among Swedish pre-school children. Thesis, Report TVBH-1015 Lund, Building Physics, LTH.

Harving, H., Korsgaard, J., Dahl, R. (1993). House-dust mites and associated environmental conditions in Danish homes. Allergy 48:106-109.

Holscher, B., Frye, C., Wichmann, H.,E.,Heinrich, J. (2002). Exposure to pets and allergies in children. Pediatr Allergy Immunol 13:334-341.

J Allergy Clin Immunol 1997;99:763-9.

Jaakola, J., Ieromnimon, A., Jaakola, M. (2006). Interior surface materials and asthma in adults: a population-based incident case-control study. Am J Epidemiol, 15;164(8):742-9.

Jaakola, J., Oie, L., Nafstad, P., Botten, G., Samuelsen, S., Magnus, P. (1999). Interior surface materials in the home and the development of bronchial obstruction in young children in Oslo, Norway. Am J Public Health 89(2):188-192

Jaakola, J., Verkasalo, P.,K., Jaakola, N. (2000). Plastic wall materials in the home and respiratory health in Young children. Am J Public Health 90(5):797-9.:

Jacob B 2002. Indoor Exposure to Molds and Allergic Sensitization Environ Health Perspect 110:647–653

Kjellman, N., I. (1977). Atopic disease in seven-year-old children. Incidence in relation to family history. Acta Peaediatr Scand. 66(4):465-71.

Lau, S., Illi, S., Sommerfeld, C., Niggemann, B., Bergmann, R., von Mutius, E., Wahn, U. (2000). Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Lancet 356:1392-7.

Le Souëf P. N. 2004. Adverse effects of maternal smoking during pregnancy on innate immunity in infants. Pediatr Pulmonol. 37:492–498.

Lee M.H., Park J., Chung S.W., Kang B.Y., Kim S.H., Kim T.S. Enhancement of Interleukin-4 Production in Activated CD4+ T Cells by Diphthalate Plasticizers via Increased NF-AT Binding Activity. International Archives of Allergy and Immunology (2004) 134: 213-222.

Lubomirova, K., Panev, T., Antova, T. (2000). Effect of ambient air pollution with organic solvents on respiratory and allergic morbidity rate in children living in the vicinity of a refinery and petrochemical plant. Hygiene and Public Health. XLIII, N 1 (in Bulgarian).

Nafstad, P., Magnus, P., Jaakola, J. (2001). Exposure to pets and atopy-related diseases in the first 4 years of life. Allergy 56:307-312.

Naydenov K., Sundell J., Melikov A., Popov T., Bornehag C.G., Stankov P. ALLHOME Project Group.(2005). "The home environment and allergies among Bulgarian children." Proceedings of Indoor Air 2005: 3574-75.

Nielsen, G.,D., Larsen, S.,T., Olsen, O., Lovik, M., Poulsen, L.,K., Glue, C., Wolkoff, P., IgE-mediated sensitisation and airway diseases. Are indoor chemicals adjuvants?. Indoor Air

Øie L., Hersoug L.G. and Madsen J.Ø. "Residential Exposure to Plasticizers and its Possible Role in the Pathogenesis of Asthma". Environmental Health Perspectives (1997) 9: 972-978.

Pattenden, S., Antova, T., Neuberger, M., Nikiforov, B., De Sario, M., Grize, L., Heinrich, J., Hruba, F., Janssen, N., Luttmann-Gibson, H., Privalova, L., Rudnai, P., Splichalova, A., Zlotkowska, R., Fletcher T. (2006). Parental smoking and childrens respiratory health: independent effects of prenatal and postnatal exposure. Tob Control 15(4):294-301.

Platts-Mills, T.,A., Erwin, E., Heymann, P., Woodfolk, J. (2005). Is the hygiene hypothesis still a viable explanation for the increased prevalence of asthma? Allergy 60:25-31.

Salam MT, Li YF, Langholz B, Gilliland FD (2004) Early-Life Environmental Risk Factors for Asthma: Findings from the Children's Health Study. Environ Health Perspect 112:760–765.

Shima, M., Adachi, M. (2000). Effect of outdoor and indoor nitrogen dioxide on respiratory symptoms in schoolchildren. Int J Epidemiol. 29:862-870.

Shore, S.,A., Johnston, R.,A. (2006). Obesity and asthma. Pharmacol Ther 110(1):83-102

Strachan, D.,P. (1989). Hay fever, hygiene, and household size. British Medical Journal, 299:1259-60.

Strachan, D.P. (2000) The role of environmental factors in asthma. Br Med Bull 56, 865-82.

Sundell, J., Wickmann, M., Pershagen, G., Nordvall, S.,L. (1995). Ventilation in homes infested by house-dust mites. Allergy 50:106-112.

Tatum, A.,J., Shapiro, G.,G. (2005). The effects of outdoor air pollution and tobacco smoke on asthma. Immunology and Allergy Clinics of North America 25(1):15-30.

The Journal of Allergy and Clinical Immunology, 2002, 110(2): 285-292).

van Odijk, J., Kull, I., Borres, M.,P., Brandtzaeg, P., Edberg, U., Hanson, L.,A., Host, A., Kuitunen, M., Olsen, S.,F., Skerfving, S., Sundell, J., Wille, S. (2003). Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966-2001) on the mode of early feeding in infancy and its impact on later allergic manifestations. Allergy 58:833-843.

Vevereux, G. (2006). The increase in the prevalence of asthma and allergy: food for thought. Nat Rev Immunol. 6(11):869-74

Wahn U. 1997. Indoor allergen exposure is a risk factor for sensitization during the first three years of life J Allergy Clin Immunol; 99:763-9

Ware, J.,H., Ferris, B.,G.,Jr, Dockery, D.,W., Spengler, J.,D., Stram, D.,O., Speitzer, F.,E. (1986). Effects of ambient sulphur oxides and suspended particles on respiratory health of preadolescent children. Am Rev Resp Dis, 133:834-842.

Wargocki, P., Sundell, J., Fanger, P.O., Gyntelberg, F., Hanssen, S.O., Harrison, P., Pickering, A., Seppanen, ell, J., Bischof, W., Brundrett, GO. and Wouters, P. (2002) Ventilation and health in non-industrial indoor environments: report from a European multidisciplinary scientific consensus meeting (EUROVEN). Indoor Air 12, 113-28

Zock JP, 2002. Housing characteristics, reported mold exposure, and asthma in the European Community Respiratory Health Survey. Journal of Allergy and Clinical Immunology, 110(2): 285-292

Cancer and indoor air quality

Forestiere F[1], Carrer P[2], Fanetti AC[2], Mc Laughlin J[3], Porta D[1], Peducci CA[1]

[1] Dept. of Epidemiology, Azienda Sanitaria Locale Roma E, Rome, Italy
[2] Dpt. of Occupational and Environmental Health, University of Milan, Italy
[3] School of Physics, University College Dublin, Dublin 4.

Introduction

Lung cancer is the most common cancer in the world and accounts for 12.3% of all new cancer in Europe. About 375,000 new cases of lung cancer were estimated for Europe in 2000; 303,000 in men and 72,000 in women. The number of deaths was about 347,000 (280,000 in men and 67,000 in women). However, there are substantial differences in incidence of lung cancer in the different regions and populations within Europe (Tyczynxki, 2003). Estimates for the year 2000 indicate that the highest age-standardized incidence rates in men (per 100,000 inhabitants) are in Hungary (95.5), Croatia (82.5), Bosnia Herzegovina (82.2) and Yugoslavia (80.9). The lowest rates are in Sweden (21.4), Iceland (31.5), Portugal (33.9) and Norway (35.1). In women the highest rates are observed in Denmark (27.7), Iceland (23.8), Hungary (22.6) and the UK (21.8). In women, the lowest incidence rates are observed in Spain (4.0), Belarus (5.0), and Portugal (5.5).

There are also differences in temporal trends. In men, lung cancer mortality is declining in Northern and Western Europe (UK and Finland), although it is already low and fairy stable in Sweden and Norway. In Central and Eastern Europe, however, lung-cancer mortality is increasing. In women, there was high and increasing mortality in the UK until the end of the 1980s. Since then, however, a plateau has been reached and rates have started to decline. In Sweden and Norway, mortality has been increasing during the past 25 years, although it is still much lower than in the UK. In Southern Europe, mortality from lung cancer is either quite low and stable in countries like Greece, or increasing at a moderate rate in Italy and Portugal.

Indoor air is contaminated by multiple pollutants generated by combustion sources, biological sources, gaseous pollutants released from household products, furnishings and building materials, and by entry of pollutants in outdoor air. These pollutants consist of a number of carcinogens, including several that have been linked to lung cancer, such as tobacco smoke (ETS), particulate matter, radon.

Epidemiological studies indicated cigarette smoking as the predominant cause of the disease, and residential radon studies estimate that radon exposure may be responsible for a not insignificant percentage of these deaths.

ETS and lung cancer

Environmental tobacco smoke (ETS) indicates the mixture of sidestream smoke and exhaled mainstream smoke that contaminates indoor air when smoking is taking place. The inhalation of ETS by nonsmokers is generally referred to as involuntary or passive smoking. The exposures of involuntary and active smoking differ quantitatively and, to some extent, qualitatively. Nevertheless, tobacco smoking in indoor environments increases levels of respirable particles, nicotine, polycyclic aromatic hydrocarbons, carbon monoxide, acroleine, and many other substances. Measurements of components of tobacco smoke in public and commercial buildings, various workplaces, and residences have shown widespread contamination by ETS. Studies using biomarkers of exposure including nicotine and its metabolite, cotinine, have further shown that ETS components are inhaled and absorbed by nonsmokers.

The adverse effects of exposure to environmental tobacco smoking (ETS) are well established (Office of Environmental Health Hazard Assessment, 2005). Several well-conducted studies have shown higher risk of coronary artery diseases, lung cancer, respiratory diseases and stroke associated with exposure to passive smoke. ETS exposure could occur in private households, work and public places. Several countries have enacted legislation that prohibit smoking in work and public places, but the interest towards policies to address exposure in households is more limited. Studies conducted in the '90 have elucidated the relationship between exposure to ETS from spouse and lung cancer risk and relative risks (RR) have been provided, resulting in 1.36 for men and 1.22 for women (Boffetta et al, 1998).
The number of lung cancer cases attributable to ETS from spouse, i.e. the Proportional Attributable Risk (PAR), was calculated in the population of the 25 EU countries aged 35+ years in the year 2000. A total of 916 (54-1928) lung cancer cases due to exposure from spouse were estimated for males and 2,449 (1,424-3,357) for females. The largest burden is for Western and Southern Europe for males (especially Germany and UK) and females (especially Germany, Italy, and France). These figures correspond to an attributable proportion of 0.5% in males and 4.6% in females (Porta, 2008).

PM and lung cancer

Particulate matter (PM) is a complex mixture of airborne solid particles and liquid droplets (aerosols) that vary in size and composition, depending upon the location and time of its source.
PM is generally divided, according to the aerodynamic diameter (D_a), into PM_{10} (D_a < 10 µm), $PM_{2.5}$ (D_a < 2.5 µm), ultrafine particles (UFPs; D_a < 100 nm). Despite its modest contribution to overall volume, the ultrafine fraction represents the largest number of particles and, therefore, presents the largest surface area.
Indoor sources of PM include fuel/tobacco combustion, cleaning operations and cooking. Moreover, fine and ultrafine particles may be formed by reactions between ozone and some VOCs Particles from outdoor air may contribute to particle load in indoor air, and exposure studies carried out in the United States and Europe showed that particles in outdoor air contributed substantially to personal exposures and to temporal variation in personal exposures, *also in the indoor environment.*
The initial suggestion that lung cancer incidence increases due to long-term exposure, low-level exposure to PM was provided by the Harvard Six Cities study (Dockery, 1993). These findings were confirmed in the long-term follow-up of the American Cancer Society, consisting of ~500,000 adults from metropolitan areas throughout the USA. Results indicated that each 10µg/m^3 elevation in PM2.5 was associated with approximately a 14% increase in lung cancer mortality(AM).
A number of European epidemiological studies on ambient air pollution and cancer published before December 2006, with focus on five analytic studies providing data on the association between various measures of particulate matter (PM) and lung cancer were recently reviewed. A case-control study of 755 men who died from lung cancer in Trieste, Italy, reported that, compared with less than 0.18 g/m/day of deposition of particulate, the relative risk (RR) was 1.1 (95% confidence interval (CI): 0.8-1.5) for 0.18-0.30 and 1.4 (95% CI: 1.1-1.8) for more than 0.30 g/m/day. In the Netherlands Cohort Study on Diet and Cancer with 60 deaths from lung cancer, the RR was 1.06 (95% CI: 0.43-2.63) for an increase of 10 mug/m in black smoke. In the French Pollution Atmospherique et Affections Respiratoires Chroniques study cohort based on 178 deaths from lung cancer, the RR associated with an increase in exposure to 10 mug/m of total suspended particulate was 0.97 (95% CI: 0.94-1.01). A nested case-control study within the European Prospective Investigation on Cancer and Nutrition included 113 nonsmokers or exsmokers diagnosed with lung cancer and 312 controls. The RRs were 0.91 (95% CI: 0.70-1.18) for an increase in PM with diameter </=10 mum (PM10) of 10 mug/m, and 0.98 (95% CI:

0.66-1.45) for exposure over 27 mug/m compared with less than 27 mug/m. In a Norwegian record linkage study, based on 1453 lung cancer deaths, no significant excess risk was found for men, and a modest association was observed for women. European studies of PM exposure and lung cancer do not show a clear association, but uncertainties remain for the measurement of exposure and latency (Gallus, 2008).

The association between long-term exposure to traffic-related air pollution and mortality was assessed in a Dutch cohort. Data were collected from an ongoing cohort study on diet and cancer with 120,852 subjects who were followed from 1987 to 1996. Exposure to black smoke (BS), nitrogen dioxide, sulfur dioxide, and particulate matter < or = 2.5 microm (PM(2.5)), as well as various exposure variables related to traffic, were estimated at the home address. Traffic intensity on the nearest road was independently associated with mortality. Relative risks for lung cancer (95% confidence intervals) for a 10-microg/m(3) increase in BS concentrations (difference between 5th and 95th percentile) were 1.03 (0.88-1.20), for a 10-microg/m(3) increase in PM concentrations were 1.06 (0.82-1.38), for a 30-microg/m(3) increase in NO_2 concentrations were 0,91 (0.72-1.15), for a 20-microg/m(3) increase in SO_2 concentrations were 1.00 (0.79-1.26) (Beelen, 2008)

Diesel motor emission is a complex mixture of hundreds of constituents in either gas or particle form. Diesel particulate matter (DPM) is composed of a center core of elemental carbon and adsorbed organic compounds including PAHs and nitro-PAHs, and small amounts of sulfate, nitrate, metals, and other trace elements. DPM consists of fine particles including a high number of ultrafine particles. These particles are highly respirable and have a large surface area where organics can adsorb easily. Exposure to DPM can cause acute irritation and neurophysiological, respiratory, and asthma-like symptoms and can exacerbate allergenic responses to known allergens. Consistently, lung cancer risk is elevated among workers in occupations where diesel engines have been used. However, quantification of the cancer risk with respect to DPM concentrations is not possible. Furthermore, ambient fine and ultrafine particles, of which DPM is an important component, contribute to cardiopulmonary morbidity and mortality and lung cancer. In conclusion, diesel exhaust poses a cancer risk greater than that of any other air pollutant, as well as causing other short- and long-term health problems. One effective way to effectively reduce emission of DPM is the use of particle traps (Wichmann, 2007).NO2 is the expression of a mixture of combustion (traffic-related) particles and gases, and is also related to power plants and waste incinerator emissions. A recent study demonstrated that 5-7% of lung cancers in European never smokers and ex-smokers are attributable to high levels of air pollution, as expressed by NO2 or proximity to heavy traffic roads (Vineis, 2007).

Cooking oil vapours and indoor coal burning

The high rates of lung cancer among female never smokers in China have led to studies evaluating the potential role of environmental factors, such as exposure to cooking oil vapours and indoor coal burning.

Traditional Chinese wok cooking involves heating cooking oils to high temperatures resulting in high levels of fume emissions, often in poorly ventilated kitchens. Volatile substances generated from cooking oils have been shown to be mutagenic and contain carcinogenic polycyclic aromatic hydrocarbons (PAHs), as well aldehydes and other mutagens. Epidemiological studies conducted in mainland China, Taiwan and Singapore have consistently demonstrated that exposure to cooking oil fumes, particularly in the absence of fume extractors, is significantly associated with an increased risk of lung cancer in Chinese women who have never smoked. Indoor coal burning for heating and cooking in homes without adequate ventilation in China has also been implicated as a risk factor. emissions from the incomplete combustion of coal have been shown to contain high concentrations of mutagenic PAHs, and mouse skin tumorigenicity studies have demonstrated that PAH-rich smoky coal emissions are ~1,000-fold more

carcinogenic than cigarette smoke. The first evidence linking indoor coal burning and lung cancer came from a 1987 study conducted in rural Xuan Wei county in China, where unusually high rates of female never smokers with lung cancer have been observed. In this study, there was a significant correlation between indoor air benzo(a)pyrene (BAP) concentration and high lung cancer mortality rates, particularly from adenocarcinoma. Subsequent large case–control studies from other regions of China have reported that household coal burning is a significant risk factor for lung cancer. Notably, exposures to these risk factors are largely preventable with the use of proper ventilation and modification of cooking practices. Indeed, a retrospective study of residents burning indoor coal in rural China found that changing from unvented fire pits to stoves with chimneys was associated with a subsequent reduction in lung cancer incidence rate (Lam, 2005)

Radon and lung cancer

from: James Mc Laughlin and Francesco Bochicchio, "Radon and lung cancer" First EnVIE Conference on Indoor Air Quality and Health for EU Policy

In the EU as in most developed regions of the world lung cancer is the most common cause of death from cancer. It is estimated that 19.7% of all cancer deaths in the EU in 2006 were due to lung cancer (Ferlay, 2007). The vast majority of these lung cancer deaths are attributable to cigarette smoking but residential radon studies estimate that radon exposure may be responsible for a not insignificant percentage of these deaths. The U.S. Surgeon General has cited radon to be the second cause of lung cancer after active smoking and radon has been classified as a Group 1 carcinogen by IARC (US Dpt. of Human Health, 2005; WHO, 1998). It has been tentatively suggested and is being investigated that radon exposure may be associated with other health endpoints but currently the only health effect established for radon is that it does cause lung cancer. Radon-222, commonly referred to as "radon", is a chemically inert radioactive gas which is a member of the Uranium-238 naturally occurring radioactive decay series. Its immediate parent in the decay series is Radium-226. It is produced in most rocks and soils from which it may enter the indoor air of houses mainly by the pressure driven ingress of soil gas. Except where building materials with elevated radium content are used generally the contribution of building materials to radon levels in indoor air is small compared to that from the soil gas.

In most of the older EU Member States extensive and representative surveys of indoor radon have taken place while in many of the recent accession countries representative nationwide indoor radon surveys have yet to take place. Table 1 gives a summary of the indoor radon data in the EU 25 expressed in units of Bq/m^3. Because of differences in the characteristics of these surveys it is not possible to calculate a population weighted EU average indoor radon concentration but it is probably close to 50 Bq/m^3. The distribution of indoor radon in most countries approximates well to a log-normal distribution. While they are very rare a small number of homes with indoor radon levels of some tens of thousands of Bq/m^3 have been found in a number of countries.

In indoor air radon produces a series of shortlived decay products which may attach to aerosol particles present in the air or deposit on room surfaces. It is the inhalation and deposition of the airborne short-lived radon decay products which gives rise to irradiation by alpha particles of sensitive cells in lung tissue such as the basal cells of the bronchial epithelium (Lubin, 1994). From considerations of their respective radioactive half lives as well as their physical and chemical properties lung dosimetry models show that the radiation dose delivered to the lung is dominated by the alpha particles emitted by the short-lived radon decay products Po-218 ($E\alpha$ = 6.00 MeV) and Po-214 ($E\alpha$ = 7.68 MeV). Because these alpha particles have respective ranges of only 48 μm and 71 μm in tissue they deliver a high density of ionization damage to cells in these

short distances. It is this lung dose that is considered to be the cause of radon induced lung cancer either on its own or jointly with tobacco smoke carcinogens.
This is supported by animal studies. Due their respective size dependent spatial deposition patterns in the human respiratory tract radon decay products unattached to aerosols (the unattached fraction) deliver a greater alpha radiation dose to sensitive lung tissue in the bronchial region compared to those attached to aerosols (the attached fraction). There have been numerous studies over past decades into the effects of elevated radon exposure on underground miners both those in uranium mines and in other types of mines (Lubin, 1994). Due to differences in study design and in particular to large errors in measuring radon and its decay products in these mines the lung cancer risk factor estimates from these studies cover a range of values. All of them, however, showed a clear dose-related increased risk due to radon exposure. Information on smoking status was available only for a fraction of miners of some of these studies. For smoker miners, the relative risk per unit radon exposure were found to be about 2–3 times higher than the relative risk for all the miners (7, National research Council, 1999). This means that the combined risk of smoking and radon was found in these studies to be submultiplicative but to be more than additive, thus suggesting synergism between radon and tobacco smoke. In absolute terms the estimated risks per unit radon exposure to smokers was found to be greater than for non-smokers in the mining cohorts.
Attempts have been made to transfer or apply the miner studies' risk factors to members of the public exposed to radon in their homes or to the general workforce in above ground workplaces but this has proved to be somewhat problematic. This is primarily because the miner studies only give estimated risks for adult male miners whose breathing rates, lung morphometry, etc, differ from that of the general population. Moreover, miners were exposed to some more risk factors for lung cancer than are the general population in their homes. In addition aerosol characteristics, degree of equilibrium between radon and its decay products and other aspects of underground mines which influence radon progeny behaviour and consequent deposition pattern in the respiratory tract differ considerably from those present in homes. Nevertheless, Lubin et al. and the U.S. National Research Council BEIR VI Committee took data on residential radon exposure in the U.S. together with data on lung cancer mortality from 11 cohorts of underground miners and on this basis estimated that the contribution from residential radon exposure to lung cancer deaths in the U.S. is in the range 10-15% (National research Council, 1999; Bochiccio, 2005). As stated above in this approach there are many sources of uncertainty in extrapolating from the miner occupational studies to the public. An alternative approach to such use of miner studies or of the more theoretical approach of lung dosimetry modeling for estimating the radon lung cancer risk to the public has been to directly determine the lung cancer risk from residential radon exposure studies.

Lung Cancer Risk From Residential Radon

Since the 1980s a number of case-control residential radon epidemiological studies have taken place in North America, in Europe and in China. A review of these can be found in (Catalan, 1999). Some of the individual studies yielded results which were equivocal. A meta-analysis, however, of the summary odds ratios for these studies showed a slightly significant association between the lung cancer risk and residential radon exposure which was consistent with the results from the occupationally exposed miner studies (Krewski, 2005). However, heterogeneity among these studies occurred, probably due to different confounding factors which cannot be controlled in a meta-analysis, whereas confounding factors can be controlled with a pooled analysis. More recently the results of a pooling of North American residential radon studies in a combined analysis of 7 North American case-control studies has been published (Darby, 2005).
In this pooling study the radon measurements were based on long-term alpha track radon detectors placed in current and former homes of study subjects. Data was gathered on modifying

factors, including age, sex, and smoking habits of the subjects. The study involved 3,662 cases of lung cancer and 4,966 controls. Collaborative analysis of individual data was carried out and data on each separate individual in the seven studies were collated centrally and analyzed with uniform methods.

The odds ratios for lung cancer were found to be increased with increasing radon exposure categories, with an odds ratio of 1.37 (0.98–1.92) for concentrations exceeding 200 Bq/m^3 relative to concentrations under 25 Bq/m^3. Using a continuous linear model to fit data, the overall estimate of the excess odds ratio for lung cancer per 100 Bq/m^3 was 11%, which was slightly significant (0%-28%). No substantial differences was observed in the excess odds ratio by categories of cigarette smoking, number smoked per day, duration of smoking, or time since quitting. The data obtained in this pooling provides direct evidence of an association between residential radon exposure and lung cancer in keeping with extrapolation from the miner studies.

In Europe a similar pooling of residential radon studies has also taken place in recent years and, like their North American counterpart, has clearly demonstrated and estimated the lung cancer risks associated with radon exposure in homes. Moreover, due to the larger total study size and the higher radon exposure levels of the European studies, a higher statistical power and therefore smaller confidence intervals were obtained and further analyses were possible to be carried out. This collaborative analysis involved 13 European epidemiological studies from nine EU Member States (Austria, Czech Republic, Finland, France, Germany, Italy, Spain, Sweden and the United Kingdom) and included individual data on 7,148 lung cancer cases and 14,208 controls without lung cancer (Darby, 2006, EC 1990). Each of these European case-control studies of residential radon and lung cancer had over 150 people with lung cancer and 150 controls without lung cancer. These studies incorporated detailed smoking histories of all subjects and sought radon measurements in homes inhabited by these individuals during the past 15 years or more. As in the North American pooling study data on each separate individual in the thirteen European studies was analyzed with uniform methods and were collated centrally. Radon measurements were obtained from residences occupied during the 5-34 year period prior to lung cancer diagnosis or acceptance as a control.

In this collaborative study a proportionate increase in risk was found not to be strongly influenced by any one study. The dose-response relationship appeared linear with no evidence of a threshold, and a significant relation remained even among those whose average measured radon concentrations were below 200 Bq/m^3. A nonregulatory Reference Level of 200 Bq/m^3 for residential radon has been in common use in some European countries for many years, originally recommended by the European Communities for future dwellings (ASH 2006). The absolute risk to smokers and recent ex-smokers was not unexpectedly found to be much greater than that to lifelong nonsmokers. This study has provided strong direct evidence of a statistically significant association of residential radon exposure and lung cancer, as predicted by extrapolation from the miner studies. The risk of lung cancer after stratification for study, age, sex, region of residence, and smoking increased by 8.4% (95% CI = 3.0%-15.8%) per 100 Bq/m^3 increase in measured radon concentration. No evidence was found that the excess relative risk varied with age, sex or smoking history. When corrections were applied to remove the bias arising from random uncertainties in radon concentration measurements, the dose-response relation was found to remain linear but increased twice in magnitude to 16% (95% CI = 5%-31%) per 100 Bq/m^3 increase of the estimated mean corrected radon concentration. While the estimated excess relative risks were independent of smoking status, in absolute terms the risks to smokers at any level of radon exposure were much greater than those to lifelong never smokers. For example, taking the risk to lifelong non-smokers exposed to a radon concentration of 0 Bq/m^3 to be 1.0 the relative risk for a habitual smoker of 15-24 cigarettes per day relative to this was estimated to be 25.8, 29.9 and 42.3 at radon concentrations of 0, 100 and 400 Bq/m^3 respectively. For lifelong non-smokers the corresponding risks are estimated to be 1.0, 1.2 and 1.6 respectively. While the

very high risks for smokers exposed to radon may seem to indicate that the risk from radon exposure is only important for smokers this is not the case. Taking the absolute lifetime risk to 75 years of lung cancer for lifelong non-smokers not exposed to radon to be about 0.41% (or 1 in 250) then on the basis of the Darby et al study for continuous exposure to radon concentrations of 400 Bq/m^3 and 800 Bq/m^3 this risk will be increased by factors of about 1.6 and 2.3 respectively. In the latter case at 800 Bq/m^3 the estimated absolute risk to a lifelong non-smoker will have increased to 0.93% (or close to 1 in 100). Even allowing for the many uncertainties in such an estimate an involuntary risk of this magnitude of contracting a fatal cancer cannot reasonably be considered to be trivial. In the context of radon and smoking it should be noted that an interaction between passive smoking and exposure to radon has also been estimated, although the combined risk would be much lower than for active smoking and with a larger confidence interval. Therefore, in this paper we will consider synergism between radon and active smoking, only. It should be noted that a pooling analysis of all the Chinese, North American and European studies which is presently underway is expected to be more informative than the previous regional ones.

In 2006 lung cancer was the most common cause of cancer death in Europe with an estimated 334,800 (19.7% of total) deaths (Feraly, 2007). Its major cause is smoking but on the basis of the Darby et al study it is estimated that in Europe, exposure to radon in the home may account for about 9% of deaths from lung cancer and 2% of all deaths from cancer (Darby, 2006). This major collaborative study of 13 residential radon epidemiological studies in 9 EU Member States therefore forms a very solid basis for policy makers both at EU and Member State levels to formulate and develop effective radon risk management strategies (EC 1990).

Estimating Radon Related Lung Cancer Deaths In the EU

The collaborative pooled analyses of epidemiological studies in North America and in Europe have provided strong evidence that residential radon is an important cause of lung cancer. The European collaborative analysis in particular has quantified the radon related risk of lung cancer to smokers and former smokers relative to that of lifelong never smokers. This study gives a firm basis in principle for estimating the burden of radon related lung cancer deaths in the EU. The process of making a realistic estimate of this burden, however, requires the existence and availability of reliable data bases on indoor radon concentrations and also of smoking prevalence in all Member States.

It should be noted in Table 1 that mean indoor radon concentrations throughout the EU are quite variable. Large variability in indoor radon concentrations may also be present within individual countries. There are many contributory factors to such variability. As indoor radon in most houses originates in the soil or rock subjacent to the house the geological and soil characteristics in a region are a strong determinant of indoor radon levels. Building design, air-tightness of houses and also ventilation preferences of the occupants can also be major influences on the indoor radon level.

These factors combined with the geographical distribution of the population in a country can also contribute to the variability. A good example is the UK where high indoor radon values are present in the Devon and Cornwall peninsula but the mean population weighted national indoor radon level at 21.7 Bq/m^3 is one of the lowest in the EU. This is primarily due to the fact that a large fraction of the UK population lives in the London region which is mainly built on clay with low radon emanating and permeability characteristics.

In the case of smoking habits the data bases available also show there is considerable variability in smoking prevalence throughout the EU. As shown in Table 2 the percentage of adults who smoke in the EU ranges from 17.5% in Sweden to 45% in Greece (Peto, 2000). The EU average is 29% but despite wide variations in smoking prevalence among member states, the overall average for the 25 member states is broadly the same as it was before enlargement in 2004.

While the average percentage of non-smoking adults in the EU can be taken from Table 2 to be 71% it should be noted that the non-smoking cohort is composed both of lifelong never smokers and former smokers. As the risk of radon related lung cancer is strongly influenced by smoking status and as the lung cancer risk decreases with time since quitting smoking in order to make a realistic estimate of radon related lung cancer incidence in the EU good information on former or ex-smokers is needed in addition to data on present active smokers (Bochicchio, 1995). Where national data on former smokers is available it usually simply given as their percentage in the population with little or no additional information such as the time since they stopped active smoking or indeed the duration and extent of their previous active smoking habits. In spite of these and other limitations in the available radon and smoking data it is possible using the findings of the Darby et al collaborative study to make an estimation of the lung cancer impact due to radon in the EU. As already stated above in this study it was estimated that in Europe, exposure to radon in the home accounts for about 9% of deaths from lung cancer and perhaps up to 2% of all deaths from cancer. More accurate estimates on the radon lung cancer burden in Europe are presently being made but are not yet completed. As lung cancer deaths in Europe are estimated to have been 334,800 in 2006 this implies that perhaps up to 30,000 of these deaths may have been caused by exposure to radon in the home (Ferlay, 2007). The corresponding estimated figures in 2006 for the EU 25 are 236,000 and about 21,000 respectively. In considering these putative radon related EU lung cancer deaths the following three important qualifying observations must be made:
(1) The majority of these estimated radon related lung related cancer deaths occur in active smokers exposed to radon.
(2) It should also be noted that, due to the near log-normal distribution of indoor radon levels found in all national surveys the majority of these deaths will occur to persons (both smokers and non-smokers) exposed to indoor radon levels well below the indoor radon Reference Level of 200 Bq/m^3 used in most European and EU countries.
(3) Residential radon studies have shown that the risk of lung cancer due to the combined effects of smoking and radon exposure are much greater than the additive effect of both individual risks. Therefore in estimating the global lung cancer burden in a country or region good data is needed on not only the indoor radon distribution but also on smoking prevalence. As Table 2 shows smoking prevalence is quite variable throughout the EU. While the EU mean is 29% the percentage of active smokers ranges from 17.5 % in Sweden to 45 % in Greece.
These three observations have important implications for policy makers in the EU formulating policies and strategies aimed at managing the lung cancer risk from indoor radon.

Mesothelioma and environmental (indoor) asbestos exposure

Mesothelioma is a rare malignant tumour of the pleura and peritoneum. The time elapsing between first exposure to asbestos and the clinical manifestation range between 20 and 40 years.
It is associated with exposure to asbestos fibres, both occupationally and in the general population.
It has long been known that non-occupational exposure to asbestos entails an increased risk of mesothelioma, both in individuals living with asbestos workers and in those living near asbestos mines, mills and factories manufacturing asbestos products. The contribution of asbestos pollution in particular in buildings built with asbestos-containing manufactures is also known.
Indoor air levels in buildings without specific asbestos sources are generally below 1000 fibres/m^3; in buildings with friable asbestos, concentrations vary irregularly and can be higher (Albin, 1999).
Information from the European cancer registries indicated that mesothelioma incidence has been increasing among men since the 1960s. According to data published in Cancer Incidence in Five

Countries-VII, 10 registries in the world (7 of which are in Europe) present cumulative incidence rates for pleural malignancy in males higher than 15 per 1000. Female rates are one order of magnitude lower than among men (Parkin, 1997).
Mesothelioma risk from domestic and environmental exposures has been studied in different European countries. Compared to other environmental exposures and to other outcomes, ascertainment of mesothelioma occurrence consequent to non occupational exposure to asbestos is facilitated by the high specificity of the association (Terracini, 2006).
Overall future incidence of mesothelioma (both due to occupational and non-occupational exposure) has been calculated by Peto et al in six European countries (Great Britain, France, Italy, Germany, Netherlands and Swiss). Deaths are expected to increase from 5000/year to 9000/year in 2018, reflecting the long latency of the disease. After that year, incidence is expected to decrease.
Occurrence of pleural malignant mesotheliomas was assessed in people who neither experienced occupational exposure to asbestos nor were married to (or known to live with) workers exposed to asbestos in the workplace. The study was conducted in North Western Italy, where a large factory produced asbestos cement up to 1985. No other major activities related to asbestos have ever been present in the area. Incidence of histologically confirmed malignant mesothelioma among residents (annual x 100,000; age adjusted) was 4.2 in men and 2.3 in women. In both sexes, rates in 1985-9 were higher than in the previous quinquennium. Corresponding estimates for 1990-1 (based on unrevised diagnoses) suggest similar rates in men and women. Rate ratios which are four to six times those measured by conventional Italian cancer registries can hardly be totally explained by bias produced by lack of recognition of occupational or paraoccupational exposure. The problem of proving this type of negative data is common to other circumstances of alleged cancer clusters of environmental (non occupational) origin (Magnani, 1995).
The contribution of exposure to asbestos through different routes in the development of mesothelioma was assessed in a study conducetd in Yorkshire. Case-control study. 185 confirmed cases of mesothelioma and 160 controls were identified, when death had occurred between 1979 and 1991 in four health districts in Yorkshire. The surviving relatives were interviewed to ascertain lifetime exposure to asbestos. Adjusted odds ratios (ORs) of exposure to asbestos (through occupational, paraoccupational, and residential routes) were calculated for cases and were compared with controls. Likely or possible occupational exposure to asbestos was more common in cases than in controls (OR 5.6, 95% confidence interval (95% CI) 3.1 to 10.1). After excluding those with likely or possible occupational exposure, likely or possible paraoccupational exposure was more common in cases than controls (OR 5.8, 95% CI 1.8 to 19.2). Only six cases of mesothelioma were identified as being solely exposed to asbestos through their residence, compared with nine controls. The OR for residential exposure to asbestos varied between 1.5 and 6.6, depending on which potential industrial sources were included, but the 95% CIs were so wide that slightly reduced or greatly increased odds comparing cases with controls could not be excluded. Results support previous evidence that occupational and paraoccupational exposure to asbestos is associated with developing mesothelioma. Despite a rigorous search, purely residential exposure seemed to account for 3% of identified cases. No firm conclusion can be drawn about the risks from residential exposure alone, as many of the study subjects could also have been occupationally or paraoccupationally exposed to asbestos. (Howel, 1999).
A population-based case-control study was carried out in six areas from Italy, Spain and Switzerland. Information was collected for 215 new histologically confirmed cases and 448 controls. A panel of industrial hygienists assessed asbestos exposure separately for occupational, domestic and environmental sources. Classification of domestic and environmental exposure was based on a complete residential history, presence and use of asbestos at home, asbestos industrial activities in the surrounding area, and their distance from the dwelling. In 53 cases and 232

controls without evidence of occupational exposure to asbestos, moderate or high probability of domestic exposure was associated with an increased risk adjusted by age and sex: odds ratio (OR) 4.81, 95% confidence interval (CI) 1.8-13.1. This corresponds to three situations: cleaning asbestos-contaminated clothes, handling asbestos material and presence of asbestos material susceptible to damage. The estimated OR for high probability of environmental exposure (living within 2000 m of asbestos mines, asbestos cement plants, asbestos textiles, shipyards, or brakes factories) was 11.5 (95% CI 3.5-38.2). Living between 2000 and 5000 m from asbestos industries or within 500 m of industries using asbestos could also be associated with an increased risk. A dose-response pattern appeared with intensity of both sources of exposure. It is suggested that low-dose exposure to asbestos at home or in the general environment carries a measurable risk of malignant pleural mesothelioma (Magnani, 2000).
Reports of mesothelioma in people from asbestos polluted areas not occupationally exposed suggest a particular susceptibility to the mineral fibre. At the same time, they also raise doubts about the existence of any threshold below which 100% of the exposed population is protected from cancer effects (Montizaan, 1989).

Conclusions
People spend most of their time indoors in buildings such as homes, offices, schools and day-care centres. Thus housing and indoor environments have important public health consequences. Important parameters in indoor environment include exposure to a large number of risk factors. These parameters are affected by human-related activities and outdoor sources (such as vehicles and industrial pollutants or local vegetation); human exposure is modified by housing characteristics such as building materials, ventilation and energy technology).

Assessment of the policy relevance of literature data

ETS
The adverse effects of exposure to environmental tobacco smoking (ETS) are well established (Office of Environmental Health Hazard Assessment, 2005). Several studies have shown higher risk of lung cancer associated with exposure to passive smoke. ETS exposure occurs in private households, work and public places. Studies conducted in the 90's have elucidated the relationship between exposure to ETS from spouse and lung cancer risk and relative risks (RR) have been provided, resulting in 1.36 for men and 1.22 for women (Boffetta et al, 1998).

Radon
It has been demonstrated by residential radon studies that exposure to radon increases the risk of lung cancer. It is estimated that for Europe radon related lung cancer deaths account for about 9 % of the total but estimates from U.S. studies put its contribution to be in the 10-15 % range.
Even though the estimated excess relative risk factor of 16% per 100 Bq/m^3 was found not to vary with age, sex or smoking history, the absolute lung cancer risk associated with unit radon exposure is much greater for active smokers than for lifelong never smokers.

PM
Evidence is emerging that long-term exposure to low concentration of PM is associated with mortality.
Recent studies provide evidence of an association between exposure to PM and increased incidence of lung cancer. At the same time, a number of studies fail to confirm such an association. The main problem affecting these type of studies is represented by exposure assessment and its consequent role in cancer development. The presence of a latency after

exposure in the onset of cancer also represents an element to be accounted for in the study design. Further observations are hence required to corroborate the hypothesis of an increased risk of lung cancer.
As to diesel exhaust exposure, there is evidence that it may pose a risk as to lung cancer development. Exposure to cooking oil vapours and indoor coal burning has been shown to be associated with an increased risk of lung cancer.

Asbestos
Environmental presence of asbestos is responsible for the onset of mesothelioma, a rare tumour, in the general population. The possibility of a transmission of asbestos fibres from buildings in the environment represents a risk for the general population; in particular for inhabitants of those buildings characterised by the use of asbestos in their construction.

Assessment of the relevance of indoor exposure threshold levels
ETS
The adverse effects of exposure to environmental tobacco smoking (ETS) are well established (Office of Environmental Health Hazard Assessment, 2005). Several studies have shown higher risk of lung cancer associated with exposure to passive smoke. ETS exposure occurs in private households, work and public places. Several countries have enacted legislation that prohibit smoking in work and public places, but the interest towards policies to address exposure in households is more limited.
PM
As to PM, exposure threshold levels are not yet specifically stated for indoor air. The American Society of Heating, Refrigerating, and Air-conditioning Engineers (ASHRAE) has adopted, for indoor air, the outdoor limits of the US-Environmental Protection Agency - National Ambient Air Quality Standards (US-EPA-NAAQS), as concern PM_{10} (150 $\mu g/m^3$/24h). This value is higher than the corresponding limit for outdoor air quality reported by WHO (92), that is 50 $\mu g/m^3$/24 h. There are no indoor standards for $PM_{2.5}$. WHO suggests, for outdoors, 25 $\mu g/m^3$/24 h and 10 $\mu g/m^3$/1 year respectively (WHO, 2000).

Radon
The most common residential radon reference level being used in EU countries is 200 Bq/m^3. This reference level is a recommended value and is not a mandatory regulatory level unlike an Action Level such as 400 or 500 Bq/m^3 for radon in workplaces set by some Member States in their implementation of the EU Basic Safety Standards Directive (18).
WHO Air Quality Guidelines for Europe also suggest that building codes should include sections to ensure that radon daughter levels do not exceed 100 Bq/m^3 EER (Equilibrium Equivalent Radon concentration) which is similar to a radon concentration of about 200 Bq/m^3.
Assessment of the potential of building envelope and HVAC system to protect people, including the susceptible individuals.

ETS
The results of the reviewed epidemiological studies underline the relevance of preventative policy to reduce indoor environmental risk factors.
Reduction of indoor air pollution requires a combination of public health policy and protective measures taken at individual levels. The actions that can be taken at political and industrial levels are the elimination of sources of pollution, when possible, and substitution of materials and equipment that are sources of pollution, with more environmental-friendly materials.

In Europe, to reduce ETS exposure, legislative measures (smoking ban or restriction in workplaces or public places) have been adopted in most countries, but no legislative interventions can be made for home or other private indoor environments, besides information campaigns for the public on both health effects by indoor pollution and maintenance of a healthy indoor environment (to avoid smoking at home, using cleaning products that do not emit polluting substances, to ensure adequate ventilation, etc.). The public-at-large is more conscious of the negative effects of bad outdoor than indoor air quality.
Cost-effective measures and technology to improve indoor air quality, available guidelines and legislation on indoor air pollution in Europe, and potential action al EU and national levels are well resumed in the report of The Towards Healthy Air in Dwellings in Europe (THADE).
Indoor risk factors are modifiable through improved ventilation, moisture control to prevent accumulation of moulds, control of the sources of pollution, e.g., tobacco smoke (avoidance of smoking indoors), combustion appliances, consumer products.

Control Options

In order to decrease indoor air pollution, measures can be implemented with various types of actions. These include mandatory and voluntary actions on international or national level.

Building codes and standards

As the buildings represent the largest share of property values in Europe it is natural that the quality of buildings is controlled with European and national building codes and standards. For the construction industry the common European standards would be beneficial. Of course the climatic and cultural differences should be considered in the standards and guidelines. Prenormative work (ALA 2001, ASHRAE 62, ASHRAE GPC10 2001, Björck 2002, Canadian standard Z204-1994, CIB 2002, ISO 2002, CEN TC 156 2002, HB 2000, Jonsen et al. 1996, Samuelsson 2000, Tuomainen 2002) done by research institutes, construction companies and professional organisations is important in this area. Building codes and standards are needed specially:
- *to improve ventilation and*
- *to control moisture in buildings.*

Consumer information

A way to implement the measures is based on voluntary actions with education and information campaigns. The patient associations like the member societies of European Federation of Allergy and Airways Diseases Patients´ Association have an important role in implementing this type of campaigns, however, the campaigns should be implemented in co-operation with professional organisations and with government support. Good experience of this type of successful campaigns is the Finnish Asthma Programme (Asthma Programme in Finland 1994-2004). The programme has been effective. Mortality and days of hospitalisation have decreased even though percentage of asthmatic persons has increased to four fold during the last twenty years. Shorter campaigns like Swedish Indoor Climate Year 1999 and Finnish Indoor Climate Information and Education Year 2002 have also been effective. Some efforts have also been done on the international level. The campaigns should focus, but not limit to the following actions:
- *to limit the exposure to environmental tobacco smoke*
- *to improving cleaning and housing hygiene*
- *to avoid the use of carpets and other harmful materials.*

PM

As to indoor generated particulate matter, measures include the control of the source, improvement of ventilation, better cleaning and housing hygiene and avoiding of carpets. The use of vacuum cleaners and central vacuum cleaning systems should be encouraged, along with the development of performance criteria for vacuum cleaners, the cleaning after or before the operation hours of the schools and offices should be encouraged.

RADON

In the case of an existing house found to be above such a reference level remedial action might involve the installation of a sub-floor sump coupled to an extractor fan or some other appropriate remedial technology, such as a radon membrane barrier, to reduce soil gas radon entry to the house living spaces (19). The cost of such remedial action will vary considerably from one house type to another but experience in some EU countries would indicate that remediation costs should be between € 500 and € 2000. In the case of future houses the incorporation of radon control building technologies into the construction is less costly than their retrofitting in existing houses and would represent a very small fraction of the cost of new house construction. The incorporation of such building technologies in all new houses is already part of the existing building codes in some EU member states such as Ireland (20). While exposure to indoor radon gives rise to a lung cancer risk this risk in principle can be controlled or reduced. At the level of an individual house it is technically feasible, in most cases, to ensure that the indoor radon level is kept at or brought down below a reference or action level set by the national radiation regulatory agencies.

Apart from these building technology aspects there are a number of different strategies that can be adopted at a national level to control indoor radon with the objective reducing the lung cancer risk associated with long term radon exposure.

These strategies may be divided into the following three principal categories:

(1) Identification of houses with high radon levels and the remediation of these houses. This is rather like the concept often used in radiation protection where a critical group of the most exposed persons is considered a protection priority and the main objective is to reduce individual high risks. In most countries a house with an indoor radon level above 1000 Bq/m^3 would be classified as “high” as the estimated lifetime lung cancer risk, even for a lifelong never smoker, would be considered unacceptable by most standards of health protection. On the basis of European national radon surveys which show that the distribution approximates closely to a log-normal distribution the percentage of dwellings in most EU states likely to have a radon level above 1000 Bq/m^3 will be very low. For example in Ireland, where the mean indoor level is 91 Bq/m^3 it is estimated that in < 0.1 % of houses is the radon level above 1000 Bq/m^3. Obviously where high houses are found at random in an area householders should be strongly advised to take action and the competent regulatory agencies should carry out more detailed local surveys to find other high houses that may be present in the area. The problems and costs of finding all high houses on a national basis would not appear in most countries to be justified both from a practical perspective and also from a costbenefit analysis perspective. On the otherhand having a strategy to find high radon houses may be justified in a defined region known to have a high radon potential due to its geological and soil characteristics.

(2) As a consequence of the characteristics of log-normal distributions and the fact that national average indoor radon levels in the EU are mostly below 100 Bq/m^3 the best strategy in principle to reduce the collective risks, i.e. the radon related number of lung cancers in the population, should be to reduce the average indoor radon level in a country. For the existing housing stock this is not a practical or cost effective option. The reduction of radon levels in new build future houses by the introduction of appropriate radon preventative building regulations is perhaps

therefore the only effective strategy that can over time effectively reduce the national risk from radon related lung cancer. In regions known to have a high radon potential particularly stringent radon prevention building regulations might be considered.
(3) Due to the demonstrated synergism between radon and smoking in terms of causing lung cancer a strategy that should be considered is to couple radon reduction strategies with national strategies aimed at reducing the consumption of cigarettes. In most EU Member States where there are well developed radon control policies a mixture of the above strategy options (1) and (2) are usually in operation together with radon risk communication programmes. However, having a combined strategy of reducing smoking and radon exposure is presently not part of the public health programme in any EU Member State.

ASBESTOS
The evidence of an association between mesothelioma and asbestos exposure is clear and highlight the need for total a ban of the fibre. In Europe, Directive 1999/77/EC banned import, export, manufacture and trade of any form of asbestos. The main problem in Europe is now related to the presence of manufactures or building containing manufactures that have not yet been removed.
In order to achieve the elimination of asbestos exposure, removal of the material from buildings represents the main measure to be adopted.
In the presence of building materials containing asbestos, a better cleaning and housing hygiene is an advisable measure in order to avoid fibre exposure.

References

ASH, Action in Smoking and Health, “Tobacco Policy in the EU”. Fact Sheet No 20, May 2006.

Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, Jerrett M, Hughes E, Armstrong B, Brunekreef B. Long-Term Effects of Traffic-Related Air Pollution on Mortal ity in a Dutch Cohort (NLCS-AIR Study). EHP 2008, 116(2):196

Bochicchio.F, Mc Laughlin.JP and Piermattei.S. “Radon in Indoor Air” 50pp, EUR16123, ISBN92-82701190, European Commission, Luxembourg, 1995.

Bochicchio.F. ”Radon epidemiology and nuclear track detectors: methods, results and perspectives”. Radiat Meas., 2005; 40: 177–190.

Boffetta P, Agudo A, Ahrens W, et al. Multicenter case-control study of exposure to environmental tabacco smoke and lung cancer in Europe. J Natl Cancer Inst 1998; 90:1440-50.

Catalan.V, Krewski.D and Zielinski.J. ”Analysis of the Combined Primary Data from Residential Radon Studies in North America: A Status Report” Extended Abstracts, Radiation Research, 1999; 151: 104-105.

Chiappino G. Mesotelioma: il ruolo delle fibre ultrafini e conseguenti riflessi in campo preventivo e medico-legale. La Medicina del Lavoro, 2005, 96,1:3-23

Commission of the European Communities. “Commission Recommendation of 21-2- 1990 on the protection of the public against indoor exposure to radon” (90/143/Euratom). Official Journal of the European Commission L 80: 26-28, 1990.

Darby.S, Hill.D, Auvinen.A et al. “Radon in homes and lung cancer risk: a collaborative analysis of individual data from 13 European case-control studies”. British Medical Journal. 2005; 330: 223-7. 210

Darby.S, Hill.D, Deo.H et al. “Residential radon and lung cancer-detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14208 persons without lung cancer from 13 epidemiologic studies in Europe”. Scandinavian Journal of Work, Environment and Health, 2006; 32, Suppl. 1, 84 pp.

Dockery, D.W., et al., An association between air pollution and mortality in six U.S. cities. N Engl J Med, 1993. 329(24): p. 1753-9.

Ferlay.J, Autier.P, Boniol.M et al. “Estimates of the cancer incidence and mortality in Europe in 2006”. Annals of Oncology, 2007; 18: 581-592.

Gallus S, Negri E, Boffetta P, McLaughlin JK, Bosetti C, La Vecchia C. European studies on long-term exposure to ambient particulate matter and lung cancer. Eur J Cancer Prev. 2008 Jun;17(3):191-4

Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. BMJ 1997; 315: 980-988.

He J, Vupputuri S, Allen K, Prerost MR, Hughes J, Whelton P. Passive smoking and the risk of coronary heart disease – A meta-analysis of epidemiologic studies. N Engl J Med 1999;340: 920-6.

Howel D, Arblaster L, Swinburn L, Schweiger M, Hatton P. Routes of asbestos exposure and the development of mesothelioma in an English region. Occup Environ Med 1997;54:403-409

Krewski.D, Lubin.J, Zielinski.J et al. “Residential radon and risk of lung cancer. A combined analysis of seven North American case-control studies”. Epidemiology, 2005, 16, 137-145.

Lam WK, 2005. Lung cancer in Asian women-the environment and genes. Respirology. 10(4):408-17.

Lubin.J, Boice.J, Edling.C et al. “Radon and lung cancer risk: a joint analysis of 11 underground miners studies.” U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, National Cancer Institute; NHI Publication No.94-3644, January 1994.

Magnani C, Agudo A, González CA, Andrion A, Calleja A, Chellini E, Dalmasso P, Escolar A, Hernandez S, Ivaldi C, Mirabelli D, Ramirez J, Turuguet D, Usel M, Terracini B. Multicentric study on malignant pleural mesothelioma and non-occupational exposure to asbestos. Br J Cancer. 2000 Jul;83(1):104-11

Magnani C, Terracini B, Ivaldi C, Botta M, Mancini A, Andrion A. Plaural malignant mesotheliomas and non-occupational exposure to asbestos in Casale Monferrato. Occup Environ Med 1995;52:362-367

Montizaan GK, Knaap AG, Van der Heijden CA. Food Chem Toxicol. 1989 Jan;27(1):53-63. Asbestos: toxicology and risk assessment for the general population in The Netherland

National Research Council. “Health Effects of Exposure to Radon” BEIR VI. Committee on the Biological Effects of Ionizing Radiation. Washington.D.C. National Academy Press, 1999.

Office of Environmental Health Hazard Assessment. California Environmental Protection Agency. Health Effects Assessment for Environmental Tobacco Smoke. 2005. http://ftp.arb.ca.gov/carbis/regact/ets2006/app3exe.pdf

Parkin DM, Whelan SL, Ferlay J, Raymond L, Lomg J. Cancer incidence in five continents. Vol VII. IARC Sci Publ 143. Lyon, 1997

Peto R, Lopez AD, Boreham J and Thun M. Mortality from smoking in developed countries 1950-2000 (2ndedition: data updated 2006) http://www.ctsu.ox.ac.uk/~tobacco/

Peto.R, Darby.S, Deo.H et al. "Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics and two case-control studies". British Medical Journal, 2000; 321: 323-329.

Porta, 2008, first Envie Conference

Terracini B. The scientific basis of a total asbestos ban. Med Lav, 2006; 97:383-392

THADE report. Franchi M, Carrer P, Kotzias D, Rameckers EMAL, Seppänen O, van Bronswijk JEMH, Viegi G. Towards Healthy Air in Dwellings in Europe. Naples, Italy 2004. http://www.efanet.org/activities/publications

Tyczynski JE, Bray F, Parkin DM. Lung Cancer in Europe in 2000: epidemiology, prevention , and early detection. Lancet Oncol 2003; 4: 45-55.

United States Department of Human Health and Services. "Surgeon General Releases National Advisory on Radon". Press release, January 13th, 2005.

Vineis, 2007. Lung cancers attributable to environmental tobacco smoke and air pollution in non-smokers in different European countries: a prospective study. Environ Health. 2007, 6:7.

WHO.http://www.who.int/tobacco/global_data/regional_databases/en/Albin M, Magnani C, Krstev S, Rapiti E, Shefer I. Asbestos and cancer: an overview of current trends in Europe. Environ Health Perspect 1999;107(suppl2):289-298.

Wichmann HE. Diesel exhaust particles. Inhal Toxicol. 2007;19 Suppl 1:241-4.

World Health Organisation, International Agency for Research on Cancer, "Manmade Mineral Fibres and Radon", IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Monograph No 43, 1988.

Chronic obstructive pulmonary disease (COPD)

Marzia Simoni, Sara Maio, Isabella Annesi-Maesano[1,2], Giovanni Viegi.

Pulmonary Environmental Epidemiology Unit - CNR Institute of Clinical Physiology, Pisa, Italy;
[1]Epidemiology of Allergic and Respiratory Department (EPAR), UMR-S 707 INSERM, Medical School St-Antoine, Paris, France;
[2]Epidemiology of Allergic and Respiratory Department (EPAR), UMR-S 707 UPMC Paris, Medical School St-Antoine, Paris, France.

Abstract

COPD is a chronic respiratory disorder responsible for a major burden to the society worldwide. Although most COPD cases are current or former smokers, a not negligible proportion of the disease also occurs in persons who have never smoked. Available data in the literature indicate that indoor pollution exposure largely affects respiratory health worldwide. Conservative estimates show that between 1.5 million and 2 million deaths per year could be attributed to indoor air pollution, with a significant proportion of deaths due to COPD. In this review of the scientific literature, we will describe relevant findings on the association of non-smoking related COPD with the exposure to more common indoor air pollutants, in adults. **Results**: Most of the findings relate to the association of COPD with passive smoke and, in developing countries, biomass combustion exposure. Both these exposures prove to be risk factors for non-smoking related COPD. Mould/dampness exposure is associated with symptoms/signs that may be related to the presence of COPD or its development. **Conclusion**: In spite of an increased COPD prevalence (predicted to further increase in the next years), and the evidence that other risk factors than smoking may be associated with COPD development, we found relatively few studies that assessed the association between COPD and common indoor air pollution in adult general population. It would be important to improve awareness on adverse health effects possibly associated with biomass combustion-related air pollution even in developed countries because of the increasing interest for wood and other biomasses as potential alternative energy sources. It is evident that there is lack of information about the relation of COPD with measured indoor levels. Studies on this topic should be performed to establish limit values for common indoor exposures, and to better focus preventative actions.

Introduction

According to World Health Organization (WHO) estimates, COPD is the fifth leading cause of global morbidity (110 million people are thought to have moderate-severe COPD) (WHO, 2007). In 2010, the disease is expected to rank as number three (Murray, 1996; Lopez, 2006). More than 3 million people died of COPD in 2005, which corresponds to 5% of all deaths globally. Total deaths from COPD are projected to increase by more than 30% in the next 10 years, unless urgent action is taken to reduce the underlying risk factors. WHO predicts that COPD will become the third leading cause of death worldwide by 2020 (WHO, 2004).

Several different definitions have been used for COPD. Historically, it has been defined symptomatically as chronic bronchitis, anatomically as emphysema, or, most recently, physiologically as airway obstruction (Halbert, 2006; Cazzola 2007). The American Thoracic Society (ATS) and the European Respiratory Society (ERS) have defined COPD as “a preventable and treatable disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette

smoking. Although COPD affects the lungs, it also produces significant systemic consequences" (Celli, 2004).

Objective demonstration of airflow obstruction by spirometry is mandatory for a diagnosis of COPD. Individuals with chronic cough/sputum production can be at risk for developing airflow obstruction. These symptoms, as well as progressive dyspnoea, are common among COPD patients, and they may precede the development of airflow limitation by many years. Thus, all adult individuals (aged >40 yrs) with chronic cough/phlegm/progressive dyspnoea, especially if smokers, should be carefully evaluated (Celli, 2004).

Variable definitions and lung function criteria for COPD have made it difficult to quantify the prevalence of the disease around the world (Viegi, 2006; Lundback, 2003; Anto, 2001). In addition, a large proportion of patients with COPD in the community remain undiagnosed. In US, about 90% of subjects with undiagnosed airflow obstruction had mild impairment and 10% moderate to severe impairment (Coultas, 2001). In Spain, among the subjects with airflow obstruction, previous diagnosis of COPD had been made in only 21.7% of cases (Miravitlles, 2005), and in UK 18.8% of COPD people were undiagnosed (Shahab, 2006). The under-recognition and under-diagnosis of COPD lead to significant under-reporting.

Halbert et al (2006) have recently published a quantitative summary of the world literature on COPD prevalence, with estimates for COPD in important subgroups defined by age, smoking status, sex, WHO region, study setting (urban or rural), and quality study. It was not possible to locate any spirometric studies reporting COPD prevalence in the African or Eastern Mediterranean regions. The pooled prevalence has been valuated 7.6%, 4.5% in Americas, 11.4% in South-East Asia, 9.0% in Western Pacific, and 7.4% in Europe. The European Lung White Book (2003) reports the prevalence of clinically relevant COPD varying in Europe from 4 to 10% of the adult population.

Active smoking is the most important risk factor for COPD. It has been estimated that about 70% of COPD related mortality is attributable to cigarette smoking (Ezzati, 2003). Other risk factors than smoking may play an important role in pathogenesis and development of chronic bronchitis and COPD (Slowik-Gabryelska, 1998). There is enough evidence that poverty, nutritional factors, age, familial and genetic factors, airway hyper-responsiveness, childhood infections, passive smoking, specific occupational exposure, outdoor and indoor air pollution are risk factors that increase the probability of developing airway obstruction, independent from smoking status (Annesi-Maesano, 2006).

Although the majority of COPD occurs in current or former smokers, a not negligible proportion of the disease also occurs in persons who have never smoked.

Halbert et al estimated a pooled prevalence of COPD diagnosis of 9.2%, in adults over 40 years and of 4.3% (95% Confidence Interval, CI 3.2-5.7) in never-smoker subjects (Halbert, 2006). Recent analyses on the Third National Health and Nutrition Examination Survey (NHANES III) data reveal that never smokers represent a significant proportion of airway obstruction in US adults (23% of obstructed subjects), and only one fifth of the obstruction in this group is explained by presence of asthma (Celli, 2005). Results by a recent Japanese Study indicate airflow obstruction in 5.8% of never-smokers (Fukuchi, 2004). Also in Europe it has been observed a sizeable proportion of never-smoker people with COPD, defined by either airflow obstruction or presence of chronic bronchitis/emphysema. In Spain, the prevalence of COPD in never-smoker people resulted 4.1% (Pena, 2000), and 23% of COPD subjects had never smoked

(Miravitlles, 2005). The prevalence of obstruction in lifelong nonsmoking subjects was 8.7% in UK (Shahab, 2006), 12% in Poland (Zielinski, 2006), and even 20.4% in Austria (Schirnhofer, 2007). In Italy, COPD in never-smokers of a general population varied when different spirometric criteria for defining COPD were used. By using the ERS criterion (FEV_1/VC <88% of predicted in males or <89% predicted in females), COPD prevalence was 10.1% in males and 10.4% in females; by using the GOLD (Global Initiative for Chronic Obstructive Lung Disease) criterion ($FEV_1/FVC<70\%$) COPD prevalence was 15.1 in men and 14.5 in females (23). In non-smoker adult Swedes, the prevalence of COPD varied from 3.4 to 24.5%, according to different spirometric cut-off points for COPD (Lindberg, 2005).

Chronic cough/phlegm was present in 16% of never-smoker Italian women selected by a general population sample (Simoni, 2007). Other Italian Study on young adults of the general population showed that 30% of the subjects with chronic cough/phlegm were never-smokers (Cerveri, 2007). In Finland, about 50% of the women with chronic bronchitis/emphysema had never regularly smoked (von Hertzen, 2000). In Sweden, chronic bronchitis/emphysema was present in about 10% of the general never-smoking population (Montnemery, 1998).

Indoor air pollution

Indoor exposure more frequently occurs at home, in social private/public settings, or in workplaces. Indoor environments contribute significantly to human exposure to pollutants, because people spend most of their time indoors. Today, indoor air pollution is globally ranked tenth among the preventable risk factors causing burden of disease (Viegi, 2004).

Common indoor pollutants and related sources are summarized in Table 1.
Available data in the literature indicate that indoor pollution exposure largely affects respiratory health worldwide. Conservative estimates show that between 1.5 million and 2 million deaths per year could be attributed to indoor air pollution, with a significant proportion of deaths due to COPD (29).

Table 1. Main indoor pollutants and related sources (Viegi, 2004).

Type	**Pollutant**	**Typical sources**
Combustion products:	*Carbon monoxide (CO)*	Gas ranges and pilot lights, unvented kerosene and gas heaters, wood and coal combustion, tobacco smoke
	Nitrogen dioxide (NO_2)	Gas ranges and pilot lights, unvented kerosene and gas heaters
	Respirable Particulate Matter (PM)	tobacco smoke, wood and coal combustion, fireplaces
	Environmental Tobacco Smoke (ETS)	Tobacco cigarettes and cigars, pipes
Volatile organic compounds (VOCs)	*- Aldehyde (formaldehyde)*	Furniture, solvents, paints, adhesives, cleaning products, tobacco smoke, insulation materials
	- Aliphatic halogenated hydrocarbons	
	- Aromatic hydrocarbons	
	- Terpenes	
Major indoor allergens	*Acarids*	
	House dust mites	Dust, bedding, carpeting
	Pets:	
	Cats or Dogs	Dandruff
	Birds	Feathers

Insects:	
Cockroaches	Floors
Fungi (moulds)	Dampness
Pollens	Plants
Rodents	Mice

The aim of this paper is to describe relevant findings, available in scientific literature, on the association of non-smoking related COPD with the exposure to more common indoor air pollutants, in adults.

Methods

We performed a review of the literature by focusing on COPD, defined as either airflow obstruction or chronic bronchitis/emphysema. Chronic cough or phlegm and dyspnoea have been also considered as health outcomes. Longitudinal studies have confirmed that cough/phlegm are linked to higher risk for COPD development. In the European Community Respiratory Health Survey (ECRHS), in subjects with chronic cough/phlegm both at baseline and at 8-years follow-up, the incidence of COPD was four-fold higher than in subjects who had never reported these symptoms at baseline (de Marco, 2007). Lindberg et al, who prospectively studied the incidence of COPD in people with normal lung function (FEV_1 (forced expiratory volume in one second)/FVC (forced vital capacity) ratio ≥ 70%) at baseline, concluded that bronchitis symptoms and dyspnoea were significant risk factors for developing COPD, and they persisted after adjustment for possible confounders (Lindberg, 2005).

We mainly considered studies on the health effects of indoor air pollution to which the general population may be commonly exposed. Specific indoor occupational exposures, that regard only some groups of workers, have been considered only marginally.

Results

In general, we found that few studies investigated the association of non-smoking related COPD with indoor air exposure. Most studies assessed the relationship between COPD and specific occupational exposure, or the health effects of ETS exposure. Biomass combustion was widely investigated as risk factor for COPD, in developing countries. Few studies evaluated the effects by directly measuring levels of pollutants. Information on such exposure has been more likely collected by interview with questions on the presence of known sources of indoor pollution.

Prevalence and incidence of COPD

Environmental tobacco smoke (ETS)

ETS is produced by tobacco combustion and contains over 4,500 compounds in both vapour and particle phases, many of them being known carcinogens and irritants. ETS is a common major source of indoor PM. Significantly higher concentration of PM has been measured in indoor places where people smoke than in smoke-free indoor environments. The effects of passive smoking have been widely investigated (Viegi, 2004). Based on the evidences in the literature, the US Environmental Protection Agency (US EPA) (1992) concluded that ETS exposure may increase the frequency of respiratory symptoms in adults, and that these effects are estimated to be 30-60% higher in ETS exposed compared to unexposed nonsmokers. Between 10 and 50% of European adults are exposed to ETS (Janson, 2001; Larsson, 2003). Preventable policy legislation has been applied in several countries to reduce ETS exposure at work and in public settings, but no legislative intervention has so far been made in dwellings. In addition, a study

performed in some European cities shows that, even in places where smoking is prohibited, the concentration of nicotine indicates that some residuals of tobacco smoke can still be found (Nebot, 2005).

Table 2 shows studies on the relation of ETS with COPD in never smokers. Chronic bronchitis was the diagnosis more frequently linked to ETS exposure, and the highest risk was reported for never smoking Chinese women exposed to ETS both in childhood and adulthood.

Table 2. Association between ETS and COPD in never smoker adults (OR=odds ratio, CI=Confidence Interval).

Author, *Source (*sample)	**Country**	**Exposure**	**Disorder**	**OR**	**95% CI**
Simoni M, *Respir Med 2007* (women)	Italy	at home and work	Dyspnoea CB/emphysema Cough/Phlegm	1.61 2.24 1.52	1.20-2.16 1.40-3.58 1.07-2.15
***Jindal SK,* Indian J Chest Dis Allied Sci 2006**	India	any	CB	1.40	1.21-1.61
David GL, *Thorax 2005*	China	in childhood and adulthood	CB Chronic Phlegm Chronic Cough	2.87 2.38 2.80	1.58-5.22 1.82-3.12 1.61-4.87
***Larsson ML,* Eur Respir J 2003**	Estonia	outside home	Dyspnoea CB/Emphysema	1.65 1.54	1.20-2.27 1.13-3.00
Radon K , *Chest 2002*	German	at work	CB	1.90	1.16-3.11
Iribarren C,* J Epidemiol Community Health 2001 *(men))	US	at home or in other places	Chronic Cough Emphysema	1.60 3.02	1.22-2.10 1.22-7.34
Jedrychowski W, *Int J Occup Environ Health 1995* (elderly women)	Poland	any	Dyspnoea	2.23	1.45-3.44
Leuenberger P, *Am J Respir Crit Care Med 1994*	Swiss	any	Dyspnoea CB	1.45 1.65	1.20-1.76 1.28-2.16
***Dayal HH* Environ Res 1994**	US	at home	ORD	1.86	1.21-2.86

CB=Chronic Bronchitis; ORD=obstructive respiratory diseases.

A recent review of the literature estimated the pooled risk for chronic cough in never smokers heavily exposed to ETS: Odds Ratios (ORs) were similar in both men (1.60, 95%CI 1.22-2.10) and women (1.68, 1.17-2.34) (Groneberg-Kloft). Significant relations between ETS exposure and COPD development have been found in the elderly, too, with an OR range of 1.68-5.63 (Jaakkola, 2002). A French study on never smoker adults found a significant inverse association

between ETS exposure and both FVC and FEV_1, with a decrement of 3.16% and 2.90%, respectively, in exposed subjects. To be exposed to ETS at home or at work represented an increased risk for abnormal low FVC (OR 2.71, 1.09-6.75) (Alipour, 2006). Also in Scotland there was evident decrement of FVC and FEV_1 in non smoker subjects exposed to ETS, when compared to unexposed ones (Chen, 2001). A dose-response effect was reported by Eisner et al, in a study on the general population in the USA: chronic bronchitis/emphysema/COPD resulted associated with higher ETS lifetime exposure at home (OR 1.55, 1.09-2.21) or at work (1.46, 1.08-1.96), after controlling for smoking history and socio-demographic characteristics (Eisner, 2005). A significant dose-related increase in the risk for developing dyspnoea has been observed in young adults for an average exposure of 10 cigarettes/day (OR 2.37, 1.25-4.51) (Jaakkola, 1996). At last, among never smoker Chinese adults, ETS exposure at home for 40 hours/a week, for more than 5 years, resulted associated with increased risk of COPD (FEV_1/FVC<70%)(OR 1.60, 1.23-2.10) (Yin, 2007).

Biomass fuels

Indoor air pollution from biomass (wood/coal) use for either cooking or heating is an important risk factor for COPD, especially in women. About 50% of world's households burn these products for cooking in open fire or with inefficient stoves in poorly ventilated rooms (Schwela, 1997). It occurs especially in developing countries, where the production of PM and CO (a proxy for $PM_{2.5}$) by biomass combustion is dramatically high (Naeher, 2001). Through an extensive review of epidemiological studies around the world, the estimation of the risk by biomass use for COPD results in in RRs of 1.8 (range 1.0-2.8) in males and 3.2 (2.3-4.8) in females (Smith, 2002). In the USA, the presence of coal stove increased the risk for chronic inflammatory and obstructive respiratory symptoms, in non smoker adults, with OR ranging from 1.8 to 3.3 (C.I. 1.0-5.9) (Xu, 1993). A selection of studies concerning the association of biomass fuel use with COPD is reported in Table 3.

Table 3. Association between biomass fuel and COPD in adults (OR=odds ratio, CI=Confidence Interval).

Author - *Source* (sample)	**Country**	**Exposure**	**Health outcome**	**OR**	**95% CI**
Liu S, *Thorax 2007* (never smoker women)(54)	China	biomass fuel	FEV_1/FVC<0.70	3.11	1.63-5.94
Orozco-Levy M, *Eur Respir J 2006* (women)(55)	Spain	wood and charcoal smoke	Dyspnoea CB	1.45 1.65	1.20-1.76 1.28-2.16
Ekici A*, Environ Res 2005 *(women) (56)	Turkey	biomass vs GPL	FEV_1/FVC<0.70 or CB	2.5	1.5-4.0
Golshan M, *Respir Med 2002* (never smoker women)(57)	Iran	biomass fuel	CB	2.91	2.08-4.40
Dennis RJ, *Chest 1996* (women)(58)	Columbia	wood-smoke	FEV_1/FVC<0.70	3.9	1.7-9.1
Xu X, *Rev Respir Dis 1993* (non smokers)(53)	China	Coal stove use: for both	Chronic Cough	1.8	1.0-3.3

	cooking and heating	Chronic Phlegm	2.0	1.2-3.4	

CB=Chronic Bronchitis; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity.

Most studies have been performed in developing countries, mainly on women. Biomass fuel use was associated with airflow obstruction in women living in Turkey, Columbia, and China. In Turkey, after adjusting for possible confounding factors, the risk for COPD, defined either as $FEV_1/FVC<0.70$ or chronic bronchitis, was higher in women using biomass fuel than in those using GPL (liquid petroleum gas), and the attributable fraction of COPD to biomass smoke was 23.1% (Ekici, 2005).

In addition (not shown in Table 3), other two studies performed in Turkey found: 1) women exposed to biomass fumes suffering more likely from chronic bronchitis and COPD than those unexposed, even though the prevalence of current smoking was higher among the latter (Kiraz, 2003); 2) never smoker housewives exposed for 30+ years to biomass fuel being at higher risk for developing COPD than those never exposed (OR 6.61, 2.17-20.18) (Sezer, 2006). In Mexico, the exposure to biomass smoke has been associated with chronic bronchitis and chronic airflow obstruction, in adults. Among never smoker women, those exposed to wood smoke had a five-fold risk as compared to the unexposed (Perez-Padilla, 1999), and women exposed domestically to biomass developed COPD with clinical characteristics, quality of life, and increased mortality similar in degree to that of tobacco smokers (Ramirez-Venegas, 2006). In China, coal smoke derived from home heating was associated with elevated reporting of persistent cough and phlegm (Qian, 2007).

Recently, Orozco-Levy et al (2006) have evidenced that biomass fuel may be a risk factor for COPD also in Europe. In their Spanish case-control study in women, exposure to wood or charcoal smoke was associated with COPD after adjusting for age and smoking. Wood or charcoal alone independently increased the risk of COPD (OR 1.8 and 1.5, respectively), but only the combination of both was statistically significant. The association between length of exposure and COPD suggested a dose-response pattern.

Mould/dampness

Building dampness may lead to emission of odorous or irritation compounds from micro-organisms or chemical degradation of building materials, such as formaldehyde (VOC).

Reported prevalence rates of home mould/dampness range widely around the world: from 10 to up 50% (Simoni, 2005).

There is evidence that long-term exposure to mould/dampness is linked to higher risk for cough, phlegm, or dyspnoea, in adults. Dales et al, in Canadian adults, found that dampness/moulds were associated with respiratory symptoms, including cough, phlegm, or dyspnoea, with an OR of 1.62 (1.48-1.68) (Dales, 1991).

1. The Institute of Medicine (IOM) of the National Academy of Sciences has published, in 2004, a critical review of the scientific literature pertaining to the association of indoor dampness and mould contamination with adverse health effect (http://books.nap.edu/catalog/11011.html). Recently, through a quantitative meta-analysis of the studies reviewed by IOM, Fisk et al estimated the pooled OR for cough in adults to be 2.10 (1.27-3.47) (Fisk, 2006).

Table 4 reports details of the studies considered in the meta-analysis. All the studies have been performed in European Nordic countries. Another study performed on Swedish adults found, by meta-analysis, that an exposure of at least 3 years to damp or mouldy odour at home was associated with persistent cough with OR ranging from 1.32 to 5.86 (95%CI from 1.22 to 6.19)(Engvall, 2001).

Table 4. Association between mould/dampness at home and cough/phlegm in adults (OR=odds ratio, CI=Confidence Interval).

Author - *Source* (sample)	**Country**	**Exposure**	**Disorder**	**OR**	**95% CI**
Brunekreef B, *Allergy 1992*	Netherland	damp	Chronic Cough:		
			men	2.56	1.94-3.38
			women	1.75	1.30-2.36
			Chronic Phlegm:		
			men	2.56	1.94-3.38
			women	1.66	1.16-2.38
Gunnbjornsdottir MI *Respir Med 2003* (youg adults)	Sweden	visible mould/ water damage	Chronic Cough	2.23	1.24-4.00
***Koskinen OM,* Eur Respir J 1999**	Finland	mould	Cough	1.60	1.01-4.01
Pirhonen I, *Eur Respir J 1996*	Finland	mould/damp	CB	1.51	0.96-1.35
			Cough	1.37	0.99-1.88
			Phlegm	1.36	1.01-1.85

CB=Chronic Bronchitis.

Gas/kerosene fuels

Some studies have evidenced associations of COPD with gas/kerosene fuel use for both heating or cooking. Gas/kerosene combustion mainly produces nitrogen dioxide and carbon monoxide. In UK, decrements in FEV_1 (-70mL) and in FVC (-35mL) have been observed in young adults using gas fuel when compared to those using electricity for cooking (Moran, 1999). In Poland, never smoker elderly women exposed to high gas cooking showed an elevated risk for dyspnoea (OR 7.16, 5.02-10.2) (Jedrychowski, 1995). In US, kerosene heaters use in never smoking women living in non smoking households was associated with increased cough (OR 1.05, 1.01-1.09)(Triche, 2005). In Italy, in a rural general population sample, the use of bottled gas for cooking was related to higher risk of chronic cough in males (OR 1.66, 1.12-2.46) and dyspnoea in males (OR 1.81, 1.15-2.85) and females (OR 1.45, 1.00-2.10)(Viegi, 1991). The association between chronic cough and use of bottled gas, instead of natural gas, was also confirmed in Italian male non smokers of a urban general population (OR 2.82, 1.12-7.10); the presence of stoves for heating (mainly non-natural gas stoves) inside the home was a risk factor for attacks of shortness of breath in non smoker women, when compared to those who lived in dwellings with central heating (stoves outside the home)(OR 1.72, 1.11-2.65)(Viegi, 1992).

Objectively measured indoor pollutants and COPD

As above reported, few studies on the relationships between COPD and indoor pollution were based on direct measurements of pollutants concentrations, except for specific occupational exposure. In Mexico, non smoking rural women, long-term exposed, when cooking, to peaks of $PM_{10} > 2.6mg/m^3$, showed a borderline significantly higher risk for having $FEV_1/FVC <70\%$ and $FEV_1<80\%$ predicted (OR 3.5, 0.94-16.3) than those exposed to lower concentration (Regalado, 2006). In China, in those exposed to elevated indoor PM_{10} level, higher prevalence of chronic cough and phlegm (Venners, 2001) and adverse effects on lung function have been observed (Pan, 2002). Effects on lung function have been found in Italy, too. In an adult general population, the exposure to high concentration of $PM_{2.5}$ resulted in both increased maximum amplitude (OR 1.38, 1.24-1.54) and diurnal variation (1.37, 1.23-1.53) of peak expiratory flow (Simoni, 2004).

Occupational exposure

A brief comment has to be devoted to specific occupational exposure. Even if it involves only specific groups of persons and can not be defined as common indoor air exposure for the general population, it often occurs in indoor environments. Occupational exposure is an important risk factor for COPD independently of tobacco smoke, and several studies report a causal association between specific work-related exposures and COPD. Dust or chemical agents to whom some categories of workers are exposed result in inflammation, a key factor in the pathogenesis of COPD. Chronic inflammation throughout the airways, parenchyma, and pulmonary vasculature are hallmarks of the disease process and lead to the pathologic changes characteristic of COPD (Ramsey, 2006). Blanc and Toren (2007), in their recent review, estimated a population attributable risk (PAR) of 15% due to occupational factors, when the outcome analyzed was either chronic bronchitis or airflow obstruction. Thus, they have confirmed the figures previously published by the ad hoc committee of the ATS (Balmes, 2003). In Spain, among the workers in the textile industry, lung function impairment resulted related to exposure duration, being independent of the effect of smoking (Jaen, 2006). Data from the ECRHS Study showed that occupational exposures to dust/fumes, vapours, or gas were risk factors for chronic cough/phlegm (relative risk ratio (RRR) 1.47, 1.31-1.65) and for COPD (by GOLD criteria, 1.62, 1.24-2.12), also after adjustment for sex, ETS exposure, smoking status, socio-economic status, and respiratory infection (de Marco, 2004). The European Farmer Study (Denmark, Germany, Switzerland, and Spain), found a COPD prevalence of 17% in never-smoker farmers working inside animal confinements buildings, and higher risk for having COPD in subjects highly exposed to indoor dust (OR 6.6, 1.1-39.5) (Monso, 2004). Finally, in Poland, among the workers in a pesticide producing factory, chronic bronchitis/emphysema or COPD (by GOLD criteria) was more prevalent in exposed to pesticides than in unexposed ones (19.3 vs 3%)(87).

COPD Exacerbations

Acute exacerbations that increase both morbidity and mortality are common among the subjects with diagnosis of COPD. Exacerbations are accompanied by increased specific symptoms (i.e. dyspnoea or phlegm), and frequently require medical intervention or hospitalization. Studies report significant relationships between acute exacerbations of COPD and exposure to increased levels of outdoor particulate pollution. Considering that indoor levels of PM may be several fold higher than outdoors, high indoor levels of PM might be associated with COPD exacerbations,

too. Indeed, among Spanish COPD patients, ETS - one of the major sources of indoor PM - was associated with increased hospital readmission for COPD exacerbations (OR 1.63, 1.04-2.57)(Garcia-Aymerich, 2003). A similar result was found in a study on US never smoker adults, who were more likely to report exacerbation of chronic respiratory disease (including chronic bronchitis and emphysema) when they were exposed to ETS (OR 1.44, 1.07-1.95) (Mannino, 1997).

Socio-economic impact of COPD

Both tangible and intangible costs (convertible and non convertible in monetary terms, respectively) of COPD are relevant. Tangible costs include direct costs (e.g. diagnostic procedures, treatment, visits, hospitalization, transfers for examinations/hospitalization…..) for the National Health Systems, and indirect costs (loss of productivity) for the society. The European Lung White Book (2003) reports that the total annual tangible cost in Europe is 38,7 billion, mostly due to lost work days (73.6% versus 12% for ambulatory care, 7.4% for hospitalizations, and 6.9% for drugs). Intangible costs are due to distress and suffering caused by COPD (patient's self-perception of health status and quality of life) are relevant, too. For example, in Italy, elderly subjects with COPD, when compared to those without the disease, reported significantly higher prevalence of activity limitation (65.7 vs 13.6), COPD related symptoms (56.6 vs 12.4), and disease impact on quality of life (51.1 vs 10.6)(90). In a recent multicentric study performed on Spanish COPD patients, the activities of daily living that were mostly affected were sport and leisure (major impact reported by 52.5%), habitual physical activity (30.3%), and sex life (20.2%)(Alvarez-Gutiérrez, 2007).
This is to point out that the social and economic burden of COPD on patients and society may be underestimated because of under-diagnosing.

Indoor pollution Standards

Control modern technology to assess indoor air quality is available for all common indoor pollutants. Unfortunately, studies on the relation between COPD (or other respiratory diseases) risk and directly measured concentration of indoor pollutants, are still poor. Thus, some exposure threshold levels are not yet stated for indoor air, specifically. The American Society of Heating, Refrigerating, and Air-conditioning Engineers (ASHRAE) has adopted, for indoor air, the outdoor limits of the US-Environmental Protection Agency - National Ambient Air Quality Standards (US-EPA-NAAQS), as concern PM_{10} (150 $\mu g/m^3$/24h) , NO_2 (100 $\mu g/m^3$/1 year), and CO (35 ppm/1 h, 9 ppm/8 h). These values are higher than corresponding limits for outdoor air quality reported by WHO (92), that are 50 $\mu g/m^3$/24 h for PM_{10}, 40 $\mu g/m^3$/1 year for NO_2 , and 25 ppm/1 h for CO. There are no indoor standards for $PM_{2.5}$. WHO suggests, for outdoors, 25 $\mu g/m^3$/24 h and 10 $\mu g/m^3$/1 year respectively (WHO, 2005). As regards to other common indoor pollutants, such as formaldheyde or moulds, ASHRAE reports specific indoor standards (100 mg/m^3/30 min and 150 CFU/m^3 - Colony Forming Units – for formaldheyde and moulds, respectively).

Prevention

The results of the reviewed epidemiological studies underline the relevance of preventative policy to reduce indoor environmental risk factors for respiratory diseases. For instance, as indicated by PAR%, the elimination of home/work ETS exposure would abate the risk for COPD of about 12% (9% for chronic cough/phlegm) in Italian never smoking women (Simoni, 2007).

A study performed in the USA found that, by eliminating work exposure to gas/vapors/fumes/dusts, the incidence of COPD would be reduced of 30% (Trupin, 2003).
Reduction of indoor air pollution requires a combination of public health policy and protective measures taken at individual levels. The actions that can be taken at political and industrial levels are the elimination of sources of pollution, when possible, and substitution of materials and equipment that are sources of pollution, with more environmental-friendly materials. In Europe, to reduce ETS exposure, legislative measures (smoking ban or restriction in workplaces or public places) have been adopted in most countries, but no legislative interventions can be made for home or other private indoor environments, besides information campaigns for the public on both health effects by indoor pollution and maintenance of a healthy indoor environment (to avoid smoking at home, using cleaning products that do not emit polluting substances, to ensure adequate ventilation, etc.). The public-at-large is more conscious of the negative effects of bad outdoor than indoor air quality.
Cost-effective measures and technology to improve indoor air quality, available guidelines and legislation on indoor air pollution in Europe, and potential action al EU and national levels are well resumed in the report of The Towards Healthy Air in Dwellings in Europe (THADE) (http://www.efanet.org/activities/publications).
Indoor risk factors are modifiable through improved ventilation, moisture control to prevent accumulation of moulds, control of the sources of pollution, e.g., tobacco smoke (avoidance of smoking indoors), combustion appliances, consumer products.
Our review clearly shows that there is a shortage of evidence-based information about COPD indoor determinants in order to better focus preventative actions. Based on currently available data it is impossible to establish safe limit values for common indoor exposures. Indoor and outdoor environments may differ in both chemical and physical characteristics (temperature, humidity…). The concentration of some pollutants may be much higher inside than outside the buildings (e.g. PM, moulds, VOC) and some pollutants may be specifically found indoors (e.g. ETS). Complex interrelationships of different pollutants at different concentrations in indoor and outdoor air may result in different health effects, particularly in more susceptible individuals, as well as elderly or diseased people, that spend most of their time inside the buildings.
Studies should be performed in general population samples on the relationship between respiratory health, including COPD, and measured indoor levels, taking into account exposure time and exposure variability. The European Union should assign research funds to address these issues. More data are needed about the effects of heating and ventilation systems, cooking appliances, ventilation rates and moisture conditions, and on the effectiveness of remedial measures.

Conclusion

In spite of increased COPD prevalence (and its predicted increasing in the next years), and of evidence that other risk factors than smoking may be associated to COPD development, we found relatively few studies that assessed the association between COPD and common indoor air pollution in adult general population, except for studies on ETS and, in developing countries, biomass combustion exposure. Both these exposures prove to be risk factors for non-smoking related COPD. It would be important to improve awareness on adverse health effects possibly associated with biomass combustion-related air pollution even in developed countries because of the increasing interest for wood and other biomasses as potential alternative energy sources. Mould/dampness exposure results associated to symptoms/signs, which may be related to the presence of COPD or its development.
To conclude, it is evident that there is lack of information about the relation of COPD with measured indoor levels. Studies on this topic should be performed to establish limit values for common indoor exposures, and to better focus preventative actions.

References

Alipour S, Deschamps F, Lesage FX. Effects of environmental tobacco smoke on respiratory symptoms and pulmonary function. Inhal Toxicol 2006;18: 569-73.

Alvarez-Gutiérrez FJ, Miravitlles M, Calle M, Gobartt E, López F, Martín A; Grupo de Estudio EIME. Impact of chronic obstructive pulmonary disease on activities of daily living: results of the EIME multicenter study. Arch Bronconeumol 2007;43:64-72.

Annesi-Maesano I. Epidemiology of chronic obstructive pulmonary disease. In : Siafakas NM : Management of Chronic Obstructive Pulmonary Disease. European Respiratory Monograph, Sheffield 2006;38:41-70.

Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, Milton D, Schwartz D, Toren K, Viegi G; Environmental and Occupational Health Assembly, American Thoracic Society . American Thoracic Society Statement: Occupational contribution to the burden of airway disease. Am J Respir Crit Care Med 2003;167: 787-97.

Blanc PD, Toren K. Occupation in chronic obstructive pulmonary disease and chronic bronchitis: an update. Int J Tuberc Lung Dis 2007;11: 251-7.

Brunekreef B. Damp housing and adult respiratory symptoms. Allergy 1992;47: 498-502.

Celli BR, Halbert RJ, Nordyke RJ, Schau B. Airway obstruction in never smokers: results from the Third National Health and Nutrition Examination Survey. Am J Med 2005;118: 1364-72.

Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23: 932-46.

Cerveri I, Accordini S, Corsico A, Zoia MC, Carrozzi L, Cazzoletti L, Beccaria M, Marinoni A, Viegi G, de Marco R; ISAYA Study Group. Chronic cough and phlegm in young adults. Eur Respir J 2003;22: 413-7.

Chen R, Tunstall-Pedoe H, Tavendale R. Environmental tobacco smoke and lung function in employees who never smoked: the Scottish MONICA study. Occup Environ Med. 2001 p;58(9):563-8

Coultas DB, Mapel D, Gagnon R, Lydick E. The health impact of undiagnosed airflow obstruction in a national sample of United States adults. Am J Respir Crit Care Med 2001;164: 372-7.

Dales RE, Burnett R, Zwanenburg H. Adverse health effects among adults exposed to home dampness and molds. Am Rev Respir Dis 1991;143: 505-9.

David GL, Koh WP, Lee HP, Yu MC, London SJ. Childhood exposure to environmental tobacco smoke and chronic respiratory symptoms in non-smoking adults: the Singapore Chinese Health Study. Thorax 2005;60: 1052-8.

Dayal HH, Khuder S, Sharrar R, Trieff N. Passive smoking in obstructive respiratory disease in an industrialized urban population. Environ. Res 1994;65: 161-71.

de Marco R, Accordini S, Cerveri I, Corsico A, Anto JM, Kunzli N, Janson C, Sunyer J, Jarvis D, Chinn S, Vermeire P, Svanes C, Ackermann-Liebrich U, Gislason T, Heinrich J, Leynaert B, Neukirch F, Schouten JP, Wjst M, Burney P. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. Am J Respir Crit Care Med 2007;175: 32-9. .

de Marco R, Accordini S, Cerveri I, Corsico A, Sunyer J, Neukirch F, Kunzli N, Leynaert B, Janson C, Gislason T, Vermeire P, Svanes C, Anto JM, Burney P; European Community Respiratory Health Survey Study Group. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. Thorax 2004;59: 120-5.

Dennis RJ, Maldonado D, Norman S, Baena E, Martinez G. Woodsmoke exposure and risk for obstructive airways disease among women. Chest 1996;109: 115-9.

Eisner MD, Balmes J, Katz PP, Trupin L, Yelin EH, Blanc PD. Lifetime environmental tobacco smoke exposure and the risk of chronic obstructive pulmonary disease. Environ Health. 2005 May 12;4(1):7.

Ekici A, Ekici M, Kurtipek E, Akin A, Arslan M, Kara T, Apaydin Z, Demir S. Obstructive airway diseases in women exposed to biomass smoke. Environ Res 2005;99: 93-8.

Engvall K, Norrby C, Norback D. Asthma symptoms in relation to building dampness and odour in older multifamily houses in Stockholm. Int J Tuberc Lung Dis 2001;5: 468-77.

European Respiratory Society. European Lung White Book: Huddersfield, European Respiratory Society Journals, Ltd; 2003.

Ezzati M, Lopez AD. Estimates of global mortality attributable to smoking in 2000. Lancet 2003;362: 847-52.

Fisk WJ, Lei-Gomez Q, Mendell MJ. Meta-Analyses of the Associations of Respiratory Health Effects with Dampness and Mold in Homes. Lawrence Berkeley National Laboratory, CA 2006;LBNL - 59363.

Fukuchi Y, Nishimura M, Ichinose M, Adachi M, Nagai A, Kuriyama T, Takahashi K, Nishimura K, Ishioka S, Aizawa H, Zaher C. COPD in Japan: the Nippon COPD Epidemiology study. Respirology 2004;9: 458-65.

Garcia-Aymerich J, Farrero E, Felez MA, Izquierdo J, Marrades RM, Anto JM; Estudi del Factors de Risc d'Aguditzacio de la MPOC investigators. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. Thorax 2003;58: 100-5.

Golshan M, Faghihi M, Marandi MM. Indoor women jobs and pulmonary risks in rural areas of Isfahan, Iran, 2000. Respir Med 2002;96: 382-8.

Groneberg-Kloft B, Feleszko W, Dinh QT, van Mark A, Brinkmann E, Pleimes D, Fischer A. Analysis and evaluation of environmental tobacco smoke exposure as a risk factor for chronic cough. Cough 2007;3: 6.

Gunnbjörnsdottir MI, Norbäck D, Plaschke P, Norrman E, Björnsson E, Janson C. The relationship between indicators of building dampness and respiratory health in young Swedish adults. Respir Med 2003;97: 302-7.

Halbert Cazzola M, Donner CF, Hanania NA. One hundred years of chronic obstructive pulmonary disease (COPD). Respir Med 2007;101: 1049-1065.

Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. Eur Respir J 2006;28: 523-32.

http://books.nap.edu/catalog/11011.html

Iribarren C, Friedman GD, Klatsky AL, Eisner MD. Exposure to environmental tobacco smoke: association with personal characteristics and self reported health conditions. J Epidemiol Community Health 2001;55: 721-8.

Jaakkola MS, Jaakkola JJ, Becklake MR, Ernst P. Effect of passive smoking on the development of respiratory symptoms in young adults: an 8-year longitudinal study.). J Clin Epidemiol 1996;49: 581-6.

Jaakkola MS. Environmental tobacco smoke and health in the elderly. Eur Respir J 2002;19: 172-81.

Jaen A, Zock JP, Kogevinas M, Ferrer A, Marin A. Occupation, smoking, and chronic obstructive respiratory disorders: a cross sectional study in an industrial area of Catalonia, Spain. Environ Health 2006;5: 2.

Janson C, Chinn S, Jarvis D, Zock JP, Toren K, Burney P; European Community Respiratory Health Survey. Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey: a cross-sectional study. Lancet 2001;358: 2103-9.

Janson Larsson ML, Loit HM, Meren M, Polluste J, Magnusson A, Larsson K, Lundback B. Passive smoking and respiratory symptoms in the FinEsS Study. Eur Respir J 2003;21: 672-6.

Jedrychowski W, Maugeri U, Gomola K, Tobiasz-Adamczyk B, Bianchi I I. Effects of Deomestic Gas Cooking and Passive Smoking on Chronic Respiratory Symptoms and Asthma in Elderly Women. Int J Occup Environ Health 1995;1: 16-20.

Jindal SK, Aggarwal AN, Chaudhry K, Chhabra SK, D'Souza GA, Gupta D, Katiyar SK, Kumar R, Shah B, Vijayan VK; Asthma Epidemiology Study Group . Tobacco smoking in India: prevalence, quit-rates and respiratory morbidity. Indian J Chest Dis Allied Sci 2006;48: 37-42.

Kiraz K, Kart L, Demir R, Oymak S, Gulmez I, Unalacak M, Ozesmi M. Chronic pulmonary disease in rural women exposed to biomass fumes. Clin Invest Med 2003;26: 243-8.

Koskinen OM, Husman TM, Meklin TM, Nevalainen AI. The relationship between moisture or mould observations in houses and the state of health of their occupants. Eur Respir J 1999;14: 1363-7.

Leuenberger P, Schwartz J, Ackermann-Liebrich U, Blaser K, Bolognini G, Bongard JP, Brandli O, Braun P, Bron C, Brutsche M. Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study). Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team. Am J Respir Crit Care Med 1994;150: 1222-8.

Lindberg A, Jonsson AC, Ronmark E, Lundgren R, Larsson LG, Lundback B. Prevalence of chronic obstructive pulmonary disease according to BTS, ERS, GOLD and ATS criteria in relation to doctor's diagnosis, symptoms, age, gender, and smoking habits. Respiration 2005;72: 471-9.

Lindberg A, Jonsson AC, Ronmark E, Lundgren R, Larsson LG, Lundback B. Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. Chest 2005;127: 1544-52.

Liu S, Zhou Y, Wang X, Wang D, Lu J, Zheng J, Zhong N, Ran P. Biomass fuels are the probable risk factor for chronic obstructive pulmonary disease in rural South China. Thorax 2007;62:889-97.

Mannino DM, Siegel M, Rose D, Nkuchia J, Etzel R. Environmental tobacco smoke exposure in the home and worksite and health effects in adults: results from the 1991 National Health Interview Survey. Tob Control 1997;6: 296-305.

Miravitlles M, Ferrer M, Pont A, Luis Viejo J, Fernando Masa J, Gabriel R, Jimenez-Ruiz CA, Villasante C, Fernandez-Fau L, Sobradillo V. Characteristics of a population of COPD patients

identified from a population-based study. Focus on previous diagnosis and never smokers. Respir Med 2005;99: 985-95.

Monso E, Riu E, Radon K, Magarolas R, Danuser B, Iversen M, Morera J, Novak D. Chronic ostructive pulmonary disease in never-smoking animal farmers working inside confinementbuildings. Am J Ind Med 2004;46: 357-62.

Montnemery P, Adelroth E, Heuman K, Johannisson A, Johansson SA, Lindholm LH, Lundback B, Lofdahl CG. Prevalence of obstructive lung diseases and respiratory symptoms in southern Sweden. Respir Med 1998;92: 1337-45.

Moran SE, Strachan DP, Johnston ID, Anderson HR. Effects of exposure to gas cooking in childhood and adulthood on respiratory symptoms, allergic sensitization and lung function in young British adults. Clin Exp Allergy 1999;29: 1033-41.

Murray C, Lopez AD. The global burden of disease. A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Boston, Harvard School of Public Health on behalf of the World Health Organisation and World Bank, 1996.

Murray Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, Schmid V, Buist S. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006; 27: 397-412.

Naeher LP, Smith KR, Leaderer BP, Neufeld L, Mage DT. Carbon monoxide as a tracer for assessing exposures to particulate matter in wood and gas cookstove households of highland Guatemala. Environ Sci Technol 2001;35: 575-81.

Narkzyc A, Sozanska E, Pierzchala W. The influence of occupational exposure to pesticides on the frequency of chronic obstructive pulmonary disease. Wiad Lek 2006;59: 596-600.

Nebot M, Lopez MJ, Gorini G, Neuberger M, Axelsson S, Pilali M, Fonseca C, Abdennbi K, Hackshaw A, Moshammer H, Laurent AM, Salles J, Georgouli M, Fondelli MC, Serrahima E, Centrich F, Hammond SK Environmental tobacco smoke exposure in public places of European cities. Tob Control 2005;14: 60-3.

Orozco-Levi M, Garcia-Aymerich J, Villar J, Ramirez-Sarmiento A, Anto JM, Gea J. Wood smoke exposure and risk of chronic obstructive pulmonary disease. Eur Respir J 2006;27: 542-6.

Pan XC, Dong Z, Wang L, Yue W. An evaluation of the indoor/outdoor air pollution and respiratory health of farmer living in rural areas Anhui Province, China. Proceedings of Indoor Air 2002;4: 982-7.

Pena VS, Miravitlles M, Gabriel R, Jimenez-Ruiz CA, Villasante C, Masa JF, Viejo JL, Fernandez-Fau L. Geographic variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study. Chest 2000;118:981-9.

Perez-Padilla JR, Regalado-Pineda J, Moran-Mendoza AO. The domestic inhalation of the smoke from firewood and of other biological materials. A risk for the development of respiratory diseases. Gac Med Mex 1999;135: 19-29.

Peruzza S, Sergi G, Vianello A, Pisent C, Tiozzo F, Manzan A, Coin A, Inelmen EM, Enzi G. Chronic obstructive pulmonary disease (COPD) in elderly subjects: impact on functional status and quality of life. Respir Med 2003;97:612-7.

Pirhonen I, Nevalainen A, Husman T, Pekkanen J. Home dampness, moulds and their influence on respiratory infections and symptoms in adults in Finland. Eur Respir J 1996;9: 2618-22.

Qian Z, He Q, Kong L, Xu F, Wei F, Chapman RS, Chen W, Edwards RD, Bascom R. Respiratory responses to diverse indoor combustion air pollution sources. Indoor Air 2007;17: 135-42.

Radon K, Büsching K, Heinrich J, Wichmann HE, Jörres RA, Magnussen H, Nowak D. Passive smoking exposure: a risk factor for chronic bronchitis and asthma in adults? Chest 2002;122: 1086-90.

Ramirez-Venegas A, Sansores RH, Perez-Padilla R, Regalado J, Velazquez A, Sanchez C, Mayar ME. Survival of patients with chronic obstructive pulmonary disease due to biomass smoke and tobacco. Am J Respir Crit Care Med 2006;173: 393-7. .

Ramsey SD, Hobbs FDR. Chronic Obstructive Pulmonary Disease, Risk Factors, and Outcome Trials Comparisons with Cardiovascular Disease. Proc Am Thorac Soc Vol 3. pp 635–640, 2006.

Regalado J, Perez-Padilla R, Sansores R, Paramo Ramirez JI, Brauer M, Pare P, Vedal S. The effect of biomass burning on respiratory symptoms and lung function in rural Mexican women. Am J Respir Crit Care Med 2006;174: 901-5. .

Schirnhofer L, Lamprecht B, Vollmer WM, Allison MJ, Studnicka M, Jensen RL, Buist AS. COPD prevalence in Salzburg, Austria: results from the Burden of Obstructive Lung Disease (BOLD) Study. Chest 2007;131:29-36.

Schwela D. Cooking smoke: a silent killer. People Planet 1997;6: 24-5.

Sezer H, Akkurt I, Guler N, Marakoglu K, Berk S. A case-control study on the effect of exposure to different substances on the development of COPD. Ann Epidemiol 2006;16:59-62.

Shahab L, Jarvis MJ, Britton J, West R. Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. Thorax 2006;61: 1043-7.

Simoni M, Baldacci S, Puntoni R, Pistelli F, Farchi S, Lo Presti E, Pistelli R, Corbo G, Agabiti N, Basso S, Matteelli G, Di Pede F, Carrozzi L, Forastiere F, Viegi G. Respiratory symptoms/diseases and environmental tobacco smoke (ETS) in never smoker Italian women. Respir Med 2007;101: 531–538.

Simoni M, Lombardi E, Berti G, Rusconi F, La Grutta S, Piffer S, Petronio MG, Galassi C, Forastiere F, Viegi G; SIDRIA-2 Collaborative Group. Mould/dampness exposure at home is associated with respiratory disorders in Italian children and adolescents: the SIDRIA-2 Study. Occup Environ Med 2005;62: 616-22.

Simoni M, Scognamiglio A, Carrozzi L, Baldacci S, Angino A, Pistelli F, Di Pede F, Viegi G. Indoor exposures and acute respiratory effects in two general population samples from a rural and an urban area in Italy. J Expo Anal Environ Epidemiol 2004;14: S144-52.

Slowik-Gabryelska A. Analysis of circumstances of the development of chronic bronchitis in patients treated at Bydgoszcz Lung Disease Clinic in 1993-1996. Pol Merkur Lekarski 1998;5: 321-4.

Smith KR, Mehta S, Feuz M. The global burden of disease from indoor air pollution: results from comparative risk assessment. Proceedings of Indoor Air 2002;IV:10-19.

Triche EW, Belanger K, Bracken MB, Beckett WS, Holford TR, Gent JF, McSharry JE, Leaderer BP. Indoor heating sources and respiratory symptoms in nonsmoking women. Epidemiology 2005;16: 377-84.

Trupin L, Earnest G, San Pedro M, Balmes JR, Eisner MD, Yelin E, Katz PP, Blanc PD. The occupational burden of chronic obstructive pulmonary disease. Eur Respir J 2003;22:462-9.

US Environmental Protection Agency. Respiratory Health effects of passive smoking: lung cancer and other disorders. Washington, DC: Office of Research and Development, EPA/600/6-90/006F, 1992.

Venners SA, Wang B, Ni J, Jin Y, Yang J, Fang Z, Xu X. Indoor air pollution and respiratory health in urban and rural China. Int J Occup Environ Health 2001;7: 173-81.

Viegi G, Carrozzi L, Paoletti P, Vellutini M, DiViggiano E, Baldacci S, Modena P, Pedreschi M, Mammini U, di Pede C. Effects of the home environment on respiratory symptoms of a general population sample in middle Italy. Arch Environ Health 1992;47: 64-70.

Viegi G, Maio S, Pistelli F, Baldacci S, Carrozzi L. Epidemiology of chronic obstructive pulmonary disease: health effects of air pollution. Respirology 2006;11: 523-32.

Viegi G, Paoletti P, Carrozzi L, Vellutini M, Ballerin L, Biavati P, Nardini G, Di Pede F, Sapigni T, Lebowitz MD. Effects of home environment on respiratory symptoms and lung function in a general population sample in north Italy. Eur Respir J 1991;4: 580-6.

Viegi G, Pedreschi M, Pistelli F, Di Pede F, Baldacci S, Carrozzi L, Giuntini C. Prevalence of airways obstruction in a general population: European Respiratory Society vs American Thoracic Society definition. Chest 2000;117: 339S-45S.

Viegi G, Simoni M, Scognamiglio A, Baldacci S, Pistelli F, Carrozzi L, Annesi-Maesano I. Indoor air pollution and airway disease. Int J Tuberc Lung Dis 2004;8: 1401-15.

Viegi Lundback Anto JM, Vermeire P, Vestbo J, Sunyer J. Epidemiology of chronic obstructive pulmonary disease. Eur Respir J 2001;17: 982-94.

Viegi Lundback B, Gulsvik A, Albers M, Bakke P, Ronmark E, van den Boom G, Brogger J, Larsson LG, Welle I, van Weel C, Omenaas E. Epidemiological aspects and early detection of chronic obstructive airway diseases in the elderly. Eur Respir J 2003;40: 3s-9s.

von Hertzen L, Reunanen A, Impivaara O, Malkia E, Aromaa A. Airway obstruction in relation to symptoms in chronic respiratory disease--a nationally representative population study. Respir Med 2000;94: 356-63.

WHO 2007, Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach.. http://www.who.int/gard

WHO World Health Organization. The World Health Report 2004: changing history. World Health Organization, Geneva, Switzerland, 2004.

WHO. Air Quality guidelines-Global update 2005.

Xu X, Wang L. Association of indoor and outdoor particulate level with chronic respiratory illness. Am Rev Respir Dis 1993;148: 1516-22.

Yin P, Jiang CQ, Cheng KK, Lam TH, Lam KH, Miller MR, Zhang WS, Thomas GN, Adab P. Passive smoking exposure and risk of COPD among adults in China: the Guangzhou Biobank Cohort Study. Lancet 2007;370:751-7.

2. Zielinski J, Bednarek M, Gorecka D, Viegi G, Hurd SS, Fukuchi Y, Lai CK, Ran PX, Ko FW, Liu SM, Zheng JP, Zhong NS, Ip MS, Vermeire PA. Increasing COPD awareness. Eur Respir J 2006;27: 833-52.

Airborne respiratory infections

Ivana Holcatova, Charles University in Prague, 1st Faculty of Medicine, Institute of Hygiene & Epidemiology, Studnickova 7, 128 00 Prague 2, Czech Republic

Introduction

Except skin, the respiratory tract is the only human organ directly affected by (indoor) air. Therefore it is understandable, that all pollutants from the air can evoke any trouble especially in susceptible people. Microbiological contamination of any environment is common and also indoor air or environment is rich in different microbes and it doesn't make too big difference if pathogenic or not as we must assume, that in common indoor environment will occur many people with immunodeficiency either due their age (ageing people's immune system is mostly weakened), their illnesses (e.g. hereditary malfunction of immune system or acquired immune malfunctions) or their treatment (people after transplantations, with lymphomas or other cancers). These so called immunocompromised people live with us, we are able to safe their lives in hospitals, so we have to guard them in indoor environment, not only hospitals but also in their homes, office buildings, schools etc.

Table 1: Worldwide mortality due to infectious diseases (WHO, 2004)

Cause of death	Deaths 2002 (millions)	% all deaths
All infectious diseases	**14.7**	**25.9%**
Lower respiratory infections	**3.9**	**6.9%**
HIV/AIDS	2.8	4.9%
Diarrhoeal diseases	1.8	3.2%
Tuberculosis (TB)	**1.6**	**2.7%**
Malaria	1.3	2.2%
Measles	**0.6**	**1.1%**
Pertussis	**0.29**	**0.5%**
Tetanus	0.21	0.4%
Meningitis	**0.17**	**0.3%**
Syphilis	0.16	0.3%
Hepatitis B	0.10	0.2%
Tropical diseases (6)	0.13	0.2%
Other causes of death include:		
maternal and perinatal conditions		*5.2%*
nutritional deficiencies		*0.9%*
noncommunicable conditions (cancer, cardiovascular diseases)		*58.8%*
injuries		*9.1%*

In second third of the 20th century people believed that infectious diseases are under control. We had got antibiotics that worked very well; vaccination programmes had fantastic effect on elimination some diseases or at least decreased a number of severe complications and total number of diseased people, especially in developed countries. One of the major killers of the world of the past centuries – smallpox – was even eradicated in the end of 70-ties.

Unfortunately beginning of eighties brought a new challenge – unknown infection agent – HIV. Other new topic followed: SARS. In last several years we are threatened with the potential avian flu mutation into epidemic one.

It seems that the Nature is still one step ahead and when we are sure of our victory, somewhere is hidden at least one new future problem. Some of these problems are results of human's activity, medical efforts or non- responsibility like bacterial strains resistant to antibiotics or Legionnaire's disease.

Regardless of our achievements on the field of infectious diseases, there are still substantial proportions of people dying of various infectious diseases (tab.1). And some of these threats are airborne infections transmitted in indoor environment.

Basics Of Infectious Diseases

Infectious agents are either obligatory pathogens (microbial agents capable of causing disease) or facultative pathogens. In fact we cannot say that any agent it NOT a pathogen as for some people and in some "concentration" (infectious dose) it should be (e.g. for immunocompromised people), so we prefer to call them facultative pathogens.

Transmission of these agents should be direct or indirect from the source. Let take into account mostly the indirect transmission from the unique source: human being. Other possibilities will be mentioned later. Whether in clinical settings, homes, schools, colleges, office buildings, theatres, or airplanes, as long as infected people cough, sneeze, shout, sing, or talk, they can discharge pathogen-filled droplets from their noses or mouths. A single sneeze alone can expel many thousands of infectious respiratory droplets into the air.

Indirect transmission is mediated by contaminated objects (of daily use like towels), by inoculation (e.g. by instruments), by alimentary way and by droplets & air – airborne infection. Although transmission via droplets is considered to be direct transmission, we can add them, for our purposes, among transmission by air. More over droplets larger than 100µm depending on their resistance to the environment can create contaminated dust. Smaller droplets can stay in air for longer or shorter time. The smaller are the droplets, the further it may be carried from the source. Small respiratory droplets that become aerosolised when people sneeze, cough, laugh or exhale can be carried by air. In addition water droplets aerosolised through air conditioning units may also spread infections. Aerosolised droplets hang in the air and are able to travel considerable distances.

With airborne transmission, direct contact with someone who is infected is not necessary to become ill. The amount of exposure necessary varies from disease to disease. Many airborne pathogens are adapted to spreading in indoor environments, where the temperature, humidity and protection from sunlight protect them in their exposed and vulnerable period when they transmit from one person to the next. For airborne infectious the main entrance of the infectious is the

respiratory tract, but for some other it could be e.g. the lesion of skin (skin infectious e.g. furuncle) or mucosa (other than in respiratory tract).

Table 2: Infectious diseases – transmission.

Disease	Infectious agent	Course of illness	Transmission	**Survival in indoor environment**
Upper-respiratory tract	Mainly viruses	Mild	Airborne - droplets	**Short**
Exantematic	Viruses	Mild (to severe)	Airborne - droplets	**Short**
Lower respiratory tract	Viruses, bacteria, etc.	Mild to severe	Airborne - droplets	**Short**
Pneumonia	Viruses, bacteria, etc.	Severe	Airborne - droplets	**Short (to long)**
Tuberculosis	*Mycobacterium tuberculosis, aviarum,* etc.	Severe	Airborne - droplets	**Long**
Legionnaire's disease	*Legionella pneumophila*	Severe	Airborne - droplets	**Long (in water)**
Pontiac fever	*Legionella pneumophila*	Mild	Airborne - droplets	**Long (in water)**
Pandemic flu	*Influenza virus*	Mild to severe	Airborne - droplets	**Short**
SARS	*SARS coronavirus*	Severe	Direct contact, airborne, droplets, oral-fecal	**Long? Re-aerosolization**
Anthrax	*Bacillus anthracis*	Severe	Airborne – pulmonary anthrax	**Very long (everywhere)**
Small pox	*Variola major*	Severe	Contact, airborne	**Long**

Indoor Threats

In indoor environment some less frequent diseases represent higher risk and higher demands on ventilation systems and environment protection not only in buildings.

Well-Known Severe (Indoor) Infections.

It is difficult or impossible to require these infections outside indoor environment or the main risk seems to be the transmission via ducts (air-condition systems, ventilation ducts, water ducts).

Tuberculosis

Chronic pulmonary **tuberculosis** caused by *Mycobacterium tuberculosis* is still, despite of the vaccination, severe threat. Over one-third of the world's population now has the TB bacterium in their bodies and new infections are occurring at a rate of one per second. Not everyone who is infected develops the disease and asymptomatic latent TB infection is most common. In developed countries is the prevalence low but in many of them the number of cases is slowly growing up in last years.

Unfortunately the percentage of resistant chains of mycobacterium is increasing and also those of atypical tuberculosis, which are very often multiresistant, too. In most European countries mortality from TB is decreasing but still in some countries (Baltic & Balkan states, but also Portugal, Poland, Finland) TB could be a problem in older age groups (EuroTB). Infectious dose (the amount of microbes necessary for developing an illness) of mycobacteria is in healthy people rather high, so transmission from person to person outdoors is difficult. Survival of agent in indoor environment is long (months).

Legionnaire's disease (Pontiac fever)

Legionellosis is a respiratory disease caused by bacteria *Legionellae*. Most frequently human disease Legionnaire's disease is caused by *L. pneumophila*. The clinical picture is characterized by myalgia, headache, fever, and non-productive cough developing further to pneumonia. Case-fatality rate can be high especially among elderly and immunocompromised individuals. Sporadic cases and outbreaks occur worldwide. In healthy, young people caused *legionella* mostly Pontiac fever – a common cold like disease with none or low risk. *Legionella* is an organism that resides in the environment in pools of stagnant water. Most common route of transmission is airborne. Person to person spread does not occur.

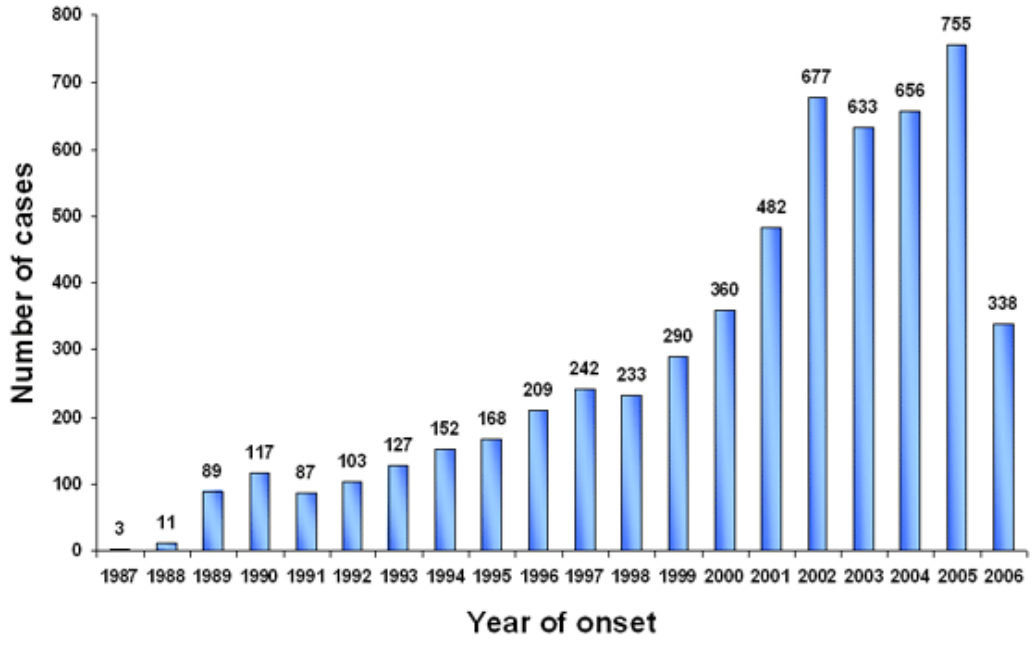
The reservoirs are aquatic systems like cooling towers, evaporative condensers, humidifiers, decorative fountains etc. Legionellosis can be treated effectively with antibiotics. Prophylactic measures include regular cleaning and maintenance of different water systems.

The European Working Group for Legionella Infections (EWGLI) was formed in 1986 with the co-ordinative centre in London. Its members are scientists with an interest in improving knowledge and information on the epidemiological and microbiological (clinical & environmental) aspects of legionnaires' disease. This is achieved through international surveillance of the disease, as well as developments in diagnosis, management and treatment methods.

The European Surveillance Scheme for Travel Associated Legionnaires' Disease (**EWGLINET**) contents the European Guidelines for Control and Prevention of Travel Associated Legionnaires' Disease. Every European country has a history of *legionella* outbreaks. Sometimes it is difficult to verify the diagnose, especially because nobody believes in it and this is the reason of constitution of this guidelines.

But not only people in hotels in tourist destinations are in risk. Unfortunately other outbreaks were described in hospitals in wards were people with severe diseases were hospitalised. These people are in higher risk than any other.

Figure 2: Graph of Legionnaire's disease cases in Europe by year of onset (EWGLINET)



The disease most often affects the elderly and people with underlying illnesses such as cancer or those with a lowered immune system. Outbreaks of pneumonia have been associated with contamination of water cooling towers in large buildings, with spread of the bacteria mostly through air conditioning systems. Nowadays the new threat comes from **tap water** during shower or aerosolization the tap water, e.g. by spraying etc., so it could be a severe problem of hospital environment.

New threats

Except these well-known problems, time to time a new one arises somewhere around the world and in a short time it could become a problem of most countries. Frequently is discussing potential epidemic of flu, which is expected for several years, and completely new agent causing SARS.

Flu

Flu pandemic is one of the threats of the end of 20th century and beginning new millenia.
Influenza virus (flu virus) cause diseases with high severity especially for elderly people, with rather high proportion of complications, worsen chronic health problems. Influenza may cause worsening of coronary heart disease or congestive heart failure. Although the incidence of influenza can vary widely between years, approximately 36,000 deaths and more than 200,000 hospitalizations are directly associated with influenza every year in America (1). Every ten to twenty years a pandemic occurs, which infects a large proportion of the world's population, and can kill tens of millions of people (2).

Last several decades a new pandemic strain is expected and there are some "promising" candidates for new reassortment. Influenza reaches peak prevalence in winter. One possible explanation for this seasonal occurrence is that, because people are indoors more often during the winter, they are in close contact more often, and this promotes transmission from person to person. Another is that cold temperatures lead to drier air, which may dehydrate mucus, preventing the body from effectively expelling virus particles.

Anyway the main problem of epidemic flu is not indoor environment as it is highly contagious infectious everywhere. In case of pandemic flu ventilation and especially air-condition systems should play the most important role in transmitting viruses or isolation sick people.

Table 3: Known flu pandemics

Name of pandemic	**Subtype involved**	**Date**	**Deaths**
Asiatic (Russian) Flu	Possibly H2N2	1889–1890	1 million
Spanish Flu	H1N1	1918–1920	40 million (100 millions)
Asian Flu	H2N2	1957–1958	1 to 1.5 million
Hong Kong Flu	H3N2	1968–1969	0.75 to 1 million

Because of high proportion of complications and even death, vaccination is recommended especially for elderly people, people with chronic disease and other immunocompromise people. Virus is extremely variable, so vaccination is necessary every year, due to antigenic drift for every year a new vaccine is necessary.

Severe acute respiratory syndrome (SARS)

In late 2002, a new syndrome was observed in southern China (Guangdong Province). It was named **severe acute respiratory syndrome (SARS)**. The initial outbreak of SARS peaked in April 2003 and by June had tailed off. By that time, there had been about 8,000 cases worldwide and 775 deaths. Respiratory distress leads to death in 3-30% of cases. Via aeroplanes was this disease transmitted to other continents. Transmission of SARS was in most cases observed in indoor environment. In fact the first outbreak was at people living at the same floor of one hotel where doctor from Guangdong province lived. Transmission was possible only via **air-conditioning system**, even airborne spread of SARS does not seem to be a major route of transmission. Also oral-fecal transmission is possible as in other coronaviruses via **sewage systems of the buildings** as coronaviruses were found also in stool of patients.

Bioterrorism

Although most of the infectious diseases are rare in 21st century in developed countries, still it is one threat of severe infections of previous centuries. Occurrence of this new threat is dating to the end of twenty century, to the nineties. This is bioterrorism. Still it is at least theoretical chance to get highly danger strains of infectious diseases like smallpox, anthrax or plaque. All these diseases were big killers of the past and are under the control in 21st century.

Yersinia pestis is the agent which causes plague, known also as Black Death. The three documented pandemics of plague (Black Death) have been responsible for the death of hundreds of millions of people. The organism in exhaled in cough droplets, infect other humans in close proximity and cause pneumonic plague, which more difficult to control and has 100% mortality. Bubonic plague is typical transmissive infection, reservoir are small rodents (well-known are rats) and vector is flea.

Anthrax is a zoonotic disease occurring in wild and domestic animals such as cattle, sheep, goats and other herbivores. It can be acquired by humans either by ingestion, **inhalation**, or skin contact with contaminated animal products. Cutaneous anthrax and gastrointestinal anthrax have lower fatality rates, but still must be treated agressively to assure survival. Because of the stability of the spore in the environment anthrax is one of the diseases commonly mentioned in relation to germ warfare and terrorist activity. In 2001 several postal workers died of inhalation anthrax after handling B. anthracis-laced.

Pulmonary anthrax results form inhalation of *Bacillus anthracis* spores which are phagocytized by the alveolar macrophages where they germinate and replicate Respiratory distress and cyanosis are manifestations of toxemia. Death results within 24 hours. This form of anthrax is of significance in biological warfare.

Smallpox (also known by the names *Variola* or *Variola vera*) is a highly contagious disease unique to humans. Smallpox is caused by either of two virus variants named *Variola major* and *Variola minor*. The deadlier form, *V. major*, has a mortality rate of 3–35%, while *V. minor* causes a milder form of disease called *alastrim* and kills ~1% of its victims. Long-term side-effects for survivors include the characteristic skin scars. Occasional side effects include blindness due to corneal ulcerations and infertility in male survivors.

Smallpox was responsible for an estimated 300–500 million deaths in the 20th century. After successful vaccination campaigns throughout the 19th and 20th centuries, the WHO certified the eradication of smallpox in 1977. In most countries the vaccination stopped around 1980, so in fact total population has no protection.

The role of indoor environment is not major but because the important route is re-aerosolization of the dust with scales from scabs, indoor environment could also play important role. Of course also special isolated wards could be highly important.

Other Diseases Of Concern (Well-known respiratory diseases)
Some of these diseases are well-known, common, we are familiar with diagnose and treatment of them. They are not harmful, at least for immunocompetent people but could be unpleasant. Many of them are easily transmitted in overcrowded interiors, environment with low air exchange or with pure quality of mechanical ventilation /air conditioning system. In environment with low level of cleaning can persisted infectious agents in dust and can be transferred into breathing zone in consequence of any activity in the environment which can whirl the dust.

These infections are not typically connected with indoor environment and improving the quality of indoor environment probably will not decrease number of sick people. On the other hand - to stop the epidemic we have to **isolate** sick people from healthy ones. Mostly from the beginning all these diseases have symptoms of common cold and rarely are threat for the life. Occurrence of these diseases is common especially from autumn to spring.

Upper respiratory tract illnesses

Cold, common cold
The common cold is caused by a large number of different types of infectious agents, especially viruses. They all result in similar symptoms: sneezing, runny nose, sore throat and cough with or without a low grade fever, muscle aches and malaise. From the medical point of view the health effect of common cold is minor, as complications are rare.
Cause of (common) cold are e.g.: Adenovirus, Coronavirus, Coxsackie A,B, Rhinovirus, Parainfluenza virus, Respiratory Syncytial Virus (RS).
Some symptoms could simulate common cold although the cause is different, e.g. Listeria monocytogenes, Legionella pneumophilla– Pontiac Fever.

Pharyngitis
Similar to cold is pharyngitis, inflammation of pharynx. The sore throat is highlighted; complications are also rare in immunocompetent people. Problems are usually caused by different species, e.g.: Adenovirus, Herpes Simplex Virus 1,2 (HHV1, HHV2), Neisseria gonorrhoeae, Parainfluenza virus, Streptococcus pyogenes.

Epiglottitis
Haemophilus influenzae is the main cause of life - threatened disease – epiglottitis. Its occurrence is connected with dry air, in young children, mostly younger than 3 years. As H. influenzae is so danger, in many countries is used vaccine against this agent.

Laryngitis
The characteristic marker of this disease is hoarseness, loss of voice and pain. Among other causes, one of the most common is Moraxella catarrhalis.

Bronchitis, bronchiolitis, bronchopneumonia
These diseases are mostly occurred as a complication of any other, originally upper respiratory tract disease. Course of the disease can vary from mild to severe depending on cause agent and status of the patient. Symptoms are as follow: fever, cough, dyspnoe, shortness of death, cyanosis. Cause (apart others) are: Moraxella catarrhalis, Parainfluenza virus, Pseudomonas aeruginosa, Respiratory Syncytial Virus (RS), Bordetella pertussis, Nocardia asteroides.

Otitis media
Otitis media is a problem mostly of young age children and often it is a complication of common cold. In very rare situation it could be danger. Chronic otitis can result in deafness and/or vertigo, in special cases can progress in mastoiditis, meningitis or encephalitis with dramatic development. The most common cause is Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pyogenes.

Lower respiratory tract illnesses
Pneumonia has the same symptoms at the beginning but mostly is more dangerous.
Typical symptoms associated with pneumonia include cough, chest pain, fever, and difficulty in breathing. Pneumonia is a common illness which occurs in all age groups, and is a leading cause of death among the elderly and people who are chronically and terminally ill. Causes of pneumonia are several and on the cause depends treatment and also prognosis. Some of the causes are: *Adenovirus, Bacteroides fragilis, Chlamydia pneumoniae, Chlamydia psitacci, Chlamydia trachomatis, Coccidioides immitis, Coronavirus, Coxiella burnetti, Cryptococcus neoformans, Cytomegalovirus* (CMV), *Escherichia coli, Haemophilus influenzae, Histoplasma*

capsulatum, Influenza virus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Listeria monocytogenes, Moraxella catarrhalis, Mycoplasma pneumoniae, Parainfluenza virus, Proteus mirabilis, Pseudomonas pseudomallei, Respiratory Syncytial Virus (RS), *Rhodococcus equi, Staphylococcus aureus, Streptococcus agalactiae, Streptococcuspneumoniae, Varicella-Zoster Virus* (HHV3).

Atypical pneumonia is sometimes difficult to diagnose when doctor have no information concerning special lifestyle or hobby (e.g. breeder of parrots). Cause agent could be various like Adenovirus, Chlamydia pneumoniae, Chlamydia psitacci, Mycoplasma pneumoniae.

Laryngotracheobronchitis or croup is a contagious viral infection causing inflammation and swelling of the larynx and surrounding tissues. It presents with difficulty in breathing especially breathing in and a typical barking cough. It usually affects children between the ages of 6 months and 3 years. Croup can be caused by a number of different viruses. In the fall, it is usually caused by Parainfluenza virus. In winter and spring, it is usually caused by Respiratory Syncytial Virus (RS) or an Influenza virus. Less commonly, croup may be caused by Measles virus or other viruses such as adenovirus, rhinovirus, enterovirus and coxsackie virus. Symptoms are typical: fever, hoarseness, harsh, barking cough, swelling - laryngeal obstruction, dyspnoe.

Herpangina is the name of a painful mouth infection caused mainly by coxsackieviruses A. Usually, herpangina is produced by one particular strain of coxsackievirus A, but it can also be caused by coxsackievirus B or echoviruses. It is most common in children. Though herpangina can be asymptomatic, symptoms usually associated are high fever and sore throat.

Other respiratory tract illnesses

Diphtheria is caused by Corynebacterium diphteriae and is characterized by an adherent membrane (a pseudomembrane) on the tonsil(s), pharynx, and/or nose. Diphtheria is a serious disease, with fatality rates between 5% and 10%. In children under 5 years and adults over 40 years, the fatality rate may be as much as 20%. Nowadays in most developed countries are children vaccinated against diphtheria.

Bordetella pertussis is the only organism of major clinical significance within this genus; it causes **whooping cough** in infants and young children. However, a closely related organism, *B. parapertussis* can also cause a milder form of bronchitis. Despite the vaccination, every 2 -5 years a small epidemic occurred, especially in young adult people, not at children.

Parrot fever is infection transmitted usually via the droppings of infected bird, though it can also be transmitted via feathers and eggs, and are typically either inhaled or ingested. Psittacosis - also known as parrot disease, parrot fever, and ornithosis - is a zoonotic infectious disease caused by a bacterium called Chlamydophila psittaci and contracted not only from parrots, but also from pigeons, sparrows, ducks, hens, sea gulls, and many other species of bird.

Meningitis

Meningitis is severe complication of various infections and despite antibiotics still kills about 170 000 persons a year (WHO, 2004). It can be caused by several agents: *Coxsackie A,B, Cryptococcus neoformans, Echovirus, Haemophilus influenzae, Herpes Simplex Virus 2* (HHV2), *Leptospita interrogans, Listeria monocytogenes,*
Moraxella catarrhalis, Neisseria meningitis, Polio virus, Streptococcus agalactiae, Streptococcus pneumonie.

Children's Exanthema Diseases
Some infections which used to be common, killed hundreds of people, especially children every year, nowadays, due to vaccination, don't present a big risk, at least in developed countries, with one exception – morbilli (measles). Because of travelling around the world, there is a possibility to meat them. Most of these infections are typical diseases of childhood. In younger age there are fewer complications than in adult people, more over vaccination against these "children" infections mostly doesn't assume booster in adult age, so specific immunity is low or lower in middle-age population. Beginning of these infections is similar – common cold and/or typical rush.

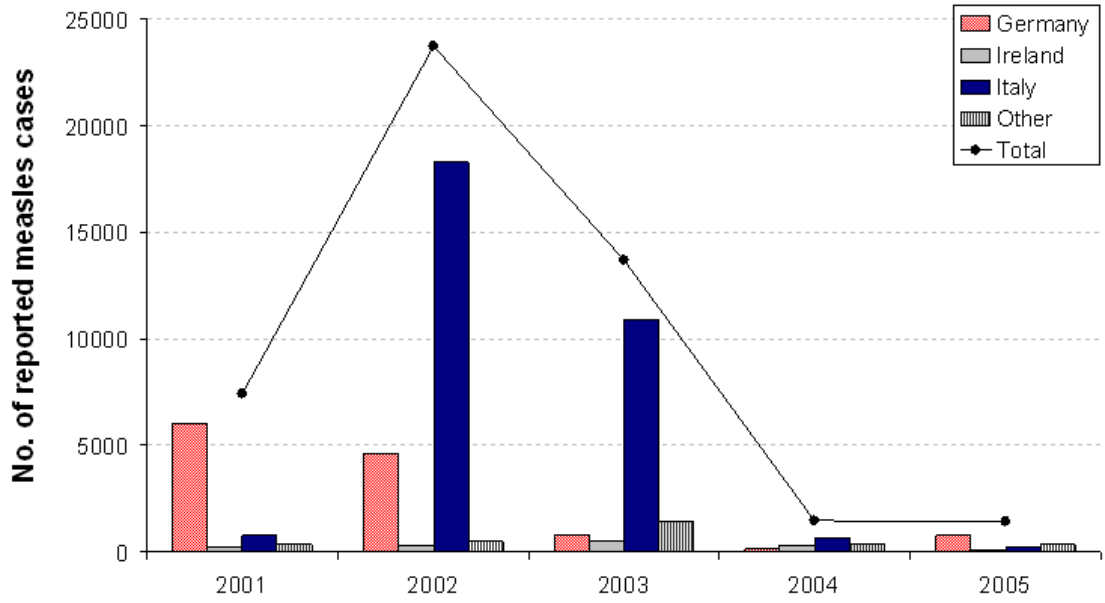
Scarlet fever was a threat because of rather frequent complication – rheumatic fever.
The disease is caused by Streptococcus pyogenes and there is a characteristic rash.
Varicella, chickenpox

Chickenpox is a highly contagious disease that spreads from person to person by direct contact or through the air from an infected person's coughing or sneezing. Chickenpox is rarely fatal but later in life viruses remaining dormant in the nerves can reactivate causing localised eruptions of shingles. This occurs particularly in people with compromised immune system, such as the elderly, and perhaps even those suffering sunburn. Unlike chickenpox which normally fully settles, shingles may result in persisting post-herpetic neuralgia pain. Because of those complications, in several countries vaccine against Varicella-Zoster Virus (HHV3), which causes varicella, is used to prevent these later complications.

Rubella (also known as epidemic roseola, German measles, liberty measles or three-day measles) is a disease caused by the Rubella Virus. It is often mild and an attack can pass unnoticed. Rubella can pose a serious risk as it can also be transmitted from a mother to her developing baby through the bloodstream via the placenta and in this case it caused teratogenic.

The **Measles** are a highly contagious airborne pathogen which spreads primarily via the respiratory system. The Measles Virus is transmitted in respiratory secretions, and can be passed from person to person via aerosol droplets containing virus particles, such as those produced by a coughing patient. Complication of measles even in childhood was severe and lethality was rather high. It was estimated that in 1996 about 1 million children died from measles complications.

Figure 1. No. of reported measles cases in 19 EUVAC.NET participating countries since 2001 (EUVAC.NET)



Mumps or epidemic parotitis is a viral disease of people causes by Mumps Virus.
Prior to the development of vaccination and the introduction of a vaccine, it was a common childhood disease worldwide, and is still a significant threat to health in the third world. Despite the vaccination, time to time a small epidemic occurrence of mumps can be observed it is danger especially in young men, because in this age the danger complications like pancreatitis or orchitis and encephalitis.

Risk Of Moulds, Yeasts (Fungi)
Very often indoor environment (or ducts) is contaminated by moulds or fungi due to poor maintenance, low air exchange etc. For healthy people this contamination doesn't represent a big harm. If any, so the risk is first of all to evaluate an allergy.
For immunocompromised people moulds could represent a life threat. Generalised or pulmonary aspergillosis can cause severe complications and even death of people with specific treatment of cancer or after transplantation.

Conclusions as to policy making

Main source of infectious agents in indoor environment are people. From that point of view is difficult to regulate source, it is not possible to have any threshold limit. But indoor environment plays important role in transmission of infectious agents – ventilation, air-conditioning, water or sewage ducts can transmit several infectious agents to rather long distances. Also overcrowded spaces increase risk of transmission of the infections agents.

1. To avoid overcrowded spaces if possible esp. in schools, health care facilities, etc.
The process of person- to- person transmission could and must be regulate especially in buildings where children and young people are concentrated, also in health-care facilities. For such buildings is suitable to use the minimal air-exchange rate per person as a sort of regulation of infections agents concentration. To achieve measured air exchange is necessary to have either

air condition systems or mechanical ventilation systems in all such buildings. Using natural ventilation is mostly subjective measure and don't guarantee the minimum air exchange especially in cities.

2. To guarantee the minimum air exchange rate in the buildings where people have to stay
Also secondary source (water, dust) can play important role even in other type of infections (alimentary – e.g. water-born cholera or some viruses causing alimentary problems). This transmission is possible to regulate also during the transmission process (limits of infection agents for drinking water, air-condition systems without water stagnation, priority of cleaning procedures of air ducts especially in health care centres and facilities for children & young people).

3. To guarantee safe water & air (limits for microbiological contamination)
There are several other facultative or obligatory pathogens with low effect for healthy people who spent their time either in well-maintained indoor environment or mostly outdoors; these agents could be harm for immunocompromised people.
One can assume that if we will be able protect ourselves against these threats, probably we will be successful also in other battles against infectious disease, either those we know or any new still unknown.

4. To achieve even better quality of the environment in health care facilities (more strict limits than for the other buildings).

References

1. Thompson, W; Shay D, Weintraub E, Brammer L, Cox N, Anderson L, Fukuda K (2003). "Mortality associated with influenza and respiratory syncytial virus in the United States". *JAMA* **289** (2): 179–86.

2. Beran, J., Havlik, J., Vonka, V.: Vaccination: History, Presence, Future. Galen, 2005 (in Czech).

3. Wallenfels, J.: Vaccination against tuberculosis. Vakcinologie, 1, 2007, pp. 28 – 45 (in Czech).

4. www.ewgli.org. The European Working Group for Legionella Infections (EWGLI) web page.

5. www.eurosurveillance.org

6. www.ecdc.europe.eu

7. www.eurotb.org. Surveillance of tuberculosis in Europe web page.

Cardiovascular effects of indoor air pollutants

Paolo Carrer [(1)], Anna Clara Fanetti [(1)], Francesco Forastiere [(2)], Serena Fossati [(1)], Christian Schlitt [(2)]

[(1)] Dpt. of Occupational and Environmental Health, Hospital L. Sacco Unit, University of Milan, Italy
[(2)] Dpt. of Epidemiology, Rome E Local Health Authority, Rome, Italy
[(3)] International Center for Pesticides and Health Risk Prevention, Hospital L. Sacco, Milan, Italy

Introduction

Cardiovascular disease is the leading cause of death in the industrialized world: CVD accounts for over 4.35 million deaths (49% of all death) each year in Europe and over 1.9 million deaths (42%) in the European Union (EU). The most common forms of cardiovascular disease are coronary heart disease (CHD) and stroke that are by themselves the two most common causes of death in the EU: accounting respectively for over 744,000 (17%) and 490,000 (11%) deaths in the EU each year. CVD mortality, incidence and case fatality are falling in most Northern, Southern and Western European Countries but either not falling as fast or rising in Central and Eastern European countries.
Overall CVD is estimated to cost the EU economy €169 billion a year. Of the total cost of CVD in the EU, around 62% is due to health care costs, 21% due to productivity losses and 17% due to the informal care of people with CVD (European cardiovascular disease statistics 2005).

The seminal Framingham Heart Study framed determinants of heart disease as “risk factors” that can quantitatively predict cardiovascular disease (Grundy et al, 1998) (Kannel, 1998). Major risk factors for CVD could be classified in fixed and modifiable. Fixed risk factors are age (older than 65), gender (male) and heredity (including race). Factors that could be modified are hypertension, high blood cholesterol levels (in particular low-density lipoprotein), diabetes mellitus (especially adult-onset or Type 2 diabetes), obesity and overweight, cigarette smoke, physical inactivity.

Besides major risk factors, other exposures, like stress and high alcohol intake (called contributing risk factors) have been associated with increased risk of cardiovascular disease, but their significance and prevalence have not yet been precisely determined.

The so called major risk factors identified in the frame of Framingham Heart Study account for a major portion of but not for the total CVD risk (Greenland, 2003 Khot, 2003). Many patients suffering from heart disease have no established risk (Heller, 1984), suggesting that quantitatively important determinants of CVD are currently unknown (Hennekens, 1998). Moreover, the identification of modifiable risk factors, such as smoking and diet, fosters the perception that the environment significantly influences cardiovascular health. This view is further reinforced by studies showing that CVD rates differ 5- to 100-fold among population groups of similar genetic background. These rates change quickly within the same ethnic group, and they increase when populations migrate from low to high-risk environments (Levi, 2002 Worth, 1975).

Despite these studies, our understanding of environmental influences has been limited to lifestyle choices such as diet, smoking, and exercise, and it is only in the last few years that disparate lines of evidences have congealed into a coherent idea that environmental exposure to pollutants and chemicals contributes to CVD risk (Bathnagar, 2004 2006).

Several studies have shown some link between outdoor PM and gases exposure and cardiovascular disease mortality and morbidity (Brook, 2004).

Indoor air pollutants that have been associated, or could be related, to an increase risk of CVD include secondhand smoke, carbon monoxide, particulate matter, ozone, nitrogen oxides, carbon monoxide and sulphur dioxide.

Secondhand smoke

Secondhand smoke (SHS), also known as environmental tobacco smoke (e.g. spousal smoking, cohabitant smoking, work exposure), is a complex mixture of gases and particles that includes smoke from the burning cigarette, cigar, or pipe tip (sidestream smoke) and exhaled mainstream smoke (National Toxicology Program. 11th Report on Carcinogens, 2005).

Many reviews have been published summarizing the epidemiological studies about the association between SHS and increase risk for CVD, here we summarized the most important and recent ones. Law and colleagues (1997) conducted a meta-analysis of all 19 studies of risk of ischemic heart disease in lifelong non-smokers who live with a smoker and in those who live with a non-smoker and concluded that people who have never smoked have an estimated 30% greater risk of ischemic heart disease if they live with a smoker, The Australian 1997 NHMRC Working Party Report (1997) reviewed the data from 22 analysis from 16 studies of SHS and CHD, finding a statistically significant increase in the risk of coronary events in nonsmokers exposed to SHS. The Californian 1997 CalEPA Report (1999) considered 10 cohort studies and 8 case-control studies of SHS and CHD and concluded that epidemiological data in Western and Eastern countries are supportive of a causal association between SHS exposure from spouses and CHD mortality in nonsmokers, in both genders. The U.S. 2001 Surgeon General's Report *Women and Smoking* (2001) reviewed 10 cohort and 10 case-control studies concluded that data from these studies support a causal association between SHS and CHD mortality, morbidity and symptoms. The U.S. 2006 Surgeon General's Report *The Health Consequences of Involuntary Exposure to Tobacco Smoke* (2006) reviewed 9 cohort and 7 case-control studies (between June 1998 and April 2002) concluded that the evidence is sufficient to infer a causal relationship between exposure to SHS and increase risk for CHD morbidity and mortality.

All these reviews concluded that the estimate risk for CHD related to SHS is about 25-30 percent and is within range of risk estimates observed for active smoking and CHD.

In the 2006 USDHHS report were also reviewed 6 studies (4 case-control, 1 cross-sectional and 1 cohort) about the association between SHS and risk of stroke, and 12 studies about the link between SHS and subclinical vascular disease, particularly carotid arterial wall thickening. The conclusion was that the analysed studies were "suggestive but not sufficient to infer a causal relationship between exposure to second hand smoke" and an increased risk of stroke and atherosclerosis (2006).

Particulate matter

Particulate matter (PM) is a complex mixture of airborne solid particles and liquid droplets (aerosols) that vary in size and composition, depending upon the location and time of its source.

PM is generally divided, according to the aerodynamic diameter (D_a), into PM_{10} ($D_a < 10$ µm), $PM_{2.5}$ ($D_a < 2.5$ µm), ultrafine particles (UFPs; $D_a < 100$ nm). Despite its modest contribution to overall volume, the ultrafine fraction represents the largest number of particles and, therefore, presents the largest surface area.

Indoor sources of PM include fuel/tobacco combustion, cleaning operations and cooking (WHO, 2005). Moreover, fine and ultrafine particles may be formed by reactions between ozone and some VOCs (the so called *indoor chemistry*), in particular terpenes. The highest terpene concentrations also produced high particle levels (Wainman, 2000 Wolkoff, 2006). Particles from outdoor air may contribute to particle load in indoor air, and exposure studies carried out in the United States and Europe showed that particles in outdoor air contributed substantially to personal exposures and to temporal variation in personal exposures, *also in the indoor environment* (Research priorities for airborne particulate matter, 2004).
The concern about indoor particulate matter cardiovascular effects arise from the epidemiological evidences of health effects of exposure to PM. During the past 15 years, the magnitude of evidence and number of studies linking outdoor air pollution to cardiovascular diseases has grown substantially (Brunekreef, 2002 Pope, 2000) and there is concern that the association of airborne particles (PM10 and PM2.5) with adverse cardiovascular outcomes is causal, as summarized in a review by a committee of the American Heart Association (Brook, 2004).
Long-term exposure to PM2.5 have been demonstrated to be independently related to cardiovascular mortality in general (Dockery, 1993), and in particular to mortality for ischemic heart disease, arrhythmia, heart failure and cardiac arrest (Pope, 2004).
Short-term effects of PM10 exposure include an increase in the overall cardiovascular mortality (Dominici, 2003 Katsouyanni 2001). Observations in Europe (Poloniecki, 1997 Hoek 2001) and North America (Burnett, 1999 Schwartz, 1999) have demonstrated higher rates of hospitalizations for all cardiovascular causes. Direct associations have also been identified with respect to incidence of ischemic heart disease, arrhythmias, and heart failure. Elevations in air pollution have also been associated with increased blood pressure during a prolonged air stagnation episode in Europe(Ibald-Mulli, 2001). Finally, recent studies from Seoul, South Korea (Hong, 2002), Taiwan (Tsai, 2003) and Kuopio, Finland (Kettunen, 2007) have reported higher incidences of ischemic strokes in direct relation to changes in ambient particle concentrations. In summary, these findings imply that short-term elevations in ambient particle levels are capable of evoking cardiac arrhythmias, worsening heart failure, and triggering acute atherosclerotic/ischemic cardiovascular complications.
To date, there have been only a limited number of studies on the association of measures of ultrafine particles with risk of cardiovascular effects (Wichmann, 2000 von Klot, 2005). The available literature suggests that ultrafine particles may induce cardiovascular health effects immediately, with a 2–4-day lag, and in association with cumulative exposures (WHO, 2005).

Carbon monoxide

Carbon monoxide is a colourless, practically odourless and tasteless gas that is poorly soluble in water, but it is soluble in alcohol and benzene. It is a product of incomplete combustion of carbon-containing fuels. Carbon monoxide burns with a violet flame and it is classified as an inorganic compound. It has a slightly lower density than air.

Toxycokynetics

After reaching the lungs, inhaled carbon monoxide diffuses rapidly across the alveolar and capillary membranes. It also readily crosses the placental membranes. Approximately 80–90% of the absorbed carbon monoxide binds with haemoglobin, which causes a reduction in the oxygen-carrying capacity of the blood. The affinity of haemoglobin for carbon monoxide is 200–250 times that for oxygen, while the relative affinities of other haem proteins (e.g. myoglobin), cytochrome oxidase and cytochrome P-450 for carbon monoxide are much lower.

When in equilibrium with ambient air, the carboxyhaemoglobin (COHb) content of the blood will depend mainly on the concentrations of inspired carbon monoxide and oxygen. If equilibrium has not been achieved, the COHb concentration will also depend on the duration of exposure, pulmonary ventilation and the COHb originally present before inhalation of the contaminated air.
Carbon monoxide is eliminated unchanged via the lungs. The decline in COHb concentration depends on the rate of carbon monoxide release from haem proteins, alveolar ventilation, oxygen concentration in inhaled air, duration of carbon monoxide exposure, and the level of COHb saturation. The formation of COHb is a reversible process, but because of the tight binding of carbon monoxide to haemoglobin, the elimination half-life while breathing room air is 2–6.5 hours depending on the initial COHb level. The elimination half-life of COHb is much longer in the fetus than in the pregnant mother (Jetter et al, 2002).

Effects of short-term exposure
CO affects health by interfering with the systemic transport of oxygen to tissues (especially the heart and other muscles and brain tissue). The resulting impairment of O2 delivery cause tissue hypoxia and interferes with cellular respiration. Direct intracellular uptake of CO could permit interactions with haemoproteins such as myoglobin, cytochrome oxidase and cytochrome P-450, and therefore interfere with electron transport processes and energy production at the cellular level. Thus, in addition to observed physiological effects and cardiovascular effects, CO can modify electron transport in nerve cells resulting in behavioural, neurological and developmental toxicological consequences, and may itself play a role in neurotransmission.

The health effects associated with inhaled CO vary with its concentration and duration of exposure. Effects range from subtle cardiovascular and neurobehavioral effects at low concentrations to unconsciousness and death after prolonged exposures or after acute exposures to high concentrations of CO.

Carbon monoxide exposure causes unintentional and suicidal poisonings, and a large number of deaths annually both in Europe and in the United States. It is estimated that more than half of the 6000 annual deaths from fires in the Unites States is caused by CO poisoning (U.S.EPA 1991). It is obvious that such homes exist where CO concentrations are high enough to increase chronic health effects, especially among sensitive populations such as pregnant women, the fetus, children, the elderly, and individuals suffering from anemia or other diseases that restrict oxygen transport between blood and cells (Ellenhorn, 1988).
Annual number of deaths due to indoor CO poisoning has decreased in Europe in the last decades, still they represent a major public health issue. Data from Italy indicate that deaths, excluding suicides, varied from 135-150 cases per year in the first part of the 80s to 40-105 cases in the very last years (ISTAT). Data from France are similar, indicating that deaths attributable to indoor CO poisoning passed from 260/280 cases in the first part of the 80s to 88/107 cases in the first years of this century (Institut de veille sanitaire).

First signs and symptoms on healthy individuals, such as decreases in work capacity and decrements of neurobehavioral functions start at (COHb) of 5%, whereas first signs of CO poisoning appear at (COHb) concentrations of 10%.
However, the variability within the human population must be considered high. A (COHb) of about 15 % only leads to slight symptoms, such as headache, in healthy adults. In contrast, the same (COHb) can cause long-lasting defects in the cognitive development and behavioural alterations in children or even contribute to death from myocardial infarction in individuals with coronary artery disease (WHO, 1999).

Cardiovascular effects

In apparently healthy subjects, the maximal exercise time and the maximal oxygen consumption have decreased at COHb levels as low as 5%. The regression between the percentage decrease in maximal oxygen consumption and the percentage increase in COHb concentration appears to be linear, with approximately a one percentage point fall in oxygen consumption per one percentage point rise in COHb level above 4% (Jetter, 2002).

Patients with cardiovascular disease, especially ischaemic heart disease, are expected to be particularly sensitive to carbon monoxide. Atherosclerotic narrowing of the coronary arteries and impaired dilatation mechanisms restrict blood flow to the myocardium and prevent physiological compensation for lowered oxygen delivery caused by elevated levels of COHb. In exercise, these subjects experience myocardial ischaemia, which can impair myocardial contractility, affect cardiac rate and rhythm, and cause angina pectoris (Jetter, 2002).

Early studies have suggested that low level carbon monoxide exposures resulting in COHb levels of 2.5–3.0% shorten the time to onset of exercise-induced chest pain in patients with angina pectoris. Subsequent studies by other investigators have actually given similar results (Jetter, 2002).

The design and results of the five most important clinical studies conducted in patients with ischaemic heart disease show that despite the obvious differences between the studies, they all refer to a significant shortening in the time to onset of angina at mean post-exposure COHb levels of 2.9–5.9% which represent mean incremental increases of 1.5–4.4% COHb from the pre-exposure baseline levels (Jetter, 2002).

The potential arrhythmogenic effects associated with low-level carbon monoxide exposures have not been fully resolved at COHb levels of ≤5% (Jetter, 2002). Hinderliter et al. (1989) reported no effects at 3.5% and 4.9% COHb levels (post-exercise concentrations) on resting and exercise-induced arrhythmias in ten patients with coronary artery disease and no baseline ectopia. In contrast, Sheps et al. (1999) showed in 41 nonsmoking patients with documented coronary artery disease and various levels of baseline ectopia that the frequencies of both single and multiple ventricular depolarizations increased significantly at a mean post-exercise COHb level of 5.0% but not at 3.5%. Dahms et al. (1993) found no additional effect of either 3% or 5% COHb over the exercise-induced increases in single or multiple ectopic beats experienced by patients with myocardial ischaemia and baseline ectopia.

According to some epidemiological and clinical data, carbon monoxide from recent smoking and environmental or occupational exposures may contribute to cardiovascular mortality and the early course of myocardial infarction (Jetter, 2002). It is not known whether this contribution is due to arrhythmogenic effects or to some longer-term effects, as suggested by some authors. In patients with severe ischaemic heart disease, carbon monoxide poisonings have been lethal at COHb levels of 10–30%, while usual COHb levels in lethal poisonings are around 50–60% (Dahms,1993).

A number of recent epidemiological studies reported associations between levels of ambient air pollutants (CO, PM, O3, NOx, SO2) and hospital admissions for cardiovascular diseases (U.S.EPA, 2000). In all the cited studies a positive association was found between CO ambient concentrations and the daily number of cardiovascular disease hospitalizations. at the local level.

Often, individuals suffering from CO poisoning are unaware of their exposure because symptoms are similar to those associated with viral illness or clinical depression (U.S.EPA,1991). This may result in a significant number of misdiagnoses by medical professionals. Although the precise number of individuals who suffer from CO poisoning is not known, it is certainly much larger than that indicated by mortality figures. It has been estimated that more than 10 000 people per year in the United States required medical attention or missed at least 1 day of work in the early 1970s because of sublethal exposures to CO. Recent esteems

indicate that over 40 000 emergency department visits annually for recognized acute CO poisoning in the United States.

Other adverse effects: developmental effects

The pregnant mother, the fetus *in utero* and the newborn infant are at high risk of adverse health effects from atmospheric carbon monoxide exposures. During pregnancy, the endogenous production of carbon monoxide can be elevated as much as 3-fold, the concentration of maternal haemoglobin is often reduced, and the mothers have physiological hyperventilation. As a result of these changes, maternal COHb levels are usually about 20% higher than the non-pregnant values. Carbon monoxide diffuses readily across the placental membranes, and the carbon-monoxidebinding affinity of fetal haemoglobin is higher than that of adult haemoglobin. Moreover, carbon monoxide is cleared much more slowly from fetal blood than from maternal blood. At steady state, fetal COHb levels are up to 10–15% higher than maternal COHb levels (Jetter, 2002).

There are theoretical reasons and supporting laboratory animal data to suggest that the fetus and the developing organs are especially vulnerable to carbon monoxide. The developing brain seems to have the highest sensitivity of all organs. There is a well established and probably causal relationship between maternal smoking and low birth weight at fetal COHb levels of 2–10%. In addition, maternal smoking seems to be associated with a dose-dependent increase in perinatal deaths and with behavioural effects in infants and young children. Carbon monoxide is probably one of the most important etiological factors for these effects, although there are numerous other toxic pollutants in tobacco smoke.

A case-control study of the association between low birthweight infants and maternal CO exposures in approximately 1000 cases in Denver failed to detect a relationship between CO exposure (estimated form fixed-site outdoor monitoring data) during the last 3 months of pregnancy and lower birth weights. Mean CO levels ranged from 0.6 to 4.1 mg/m^3 (0.5 to 3.6 ppm) at 8 monitoring locations in metropolitan Denver. The 5th and 95^{th} percentile concentrations at the site with the highest (4.1 mg/m^3) mean were 1.8 and 5.5 mg/m^3 (1.6 and 4.8 ppm), respectively. The odds ratio at the highest concentration site was 1.1 and the 95% confidence interval was 0.8-1.6. This study did not directly account for unmeasured sources of CO exposure, such as smoking, emissions from gas appliances and exposures to vehicular exhaust, which are limitations of the study design.

A more extensive study of a cohort of 125573 children born to women living in the Los Angeles area (1989-1993) found that exposure to ambient concentrations > 6.3 mg/m^3 (3 mo average) during the last trimester of pregnancy was associated with a significantly increased risk of low birthweight (odds ratio = 1.22; confidence interval =1.03-1.44) after adjustment for potential confounders (Mann, 2002). Fetotoxicity has been demonstrated in laboratory animal studies. Altered brain neurochemical development and growth retardation have been demonstrated in rats exposed to CO in utero (Ritz, 1999).

Other adverse effects: neurological and neurobehavioural effects

Central nervous system (CNS) effects in individuals suffering acute CO poisoning cover a wide range, depending on severity of exposure: headache, dizziness, weakness, nausea, vomiting, disorientation, confusion, collapse, and coma.

At low concentrations, CNS effects include reduction in visual perception, manual dexterity, learning, driving performance, and attention level. Earlier work is frequently cited to justify the statement that CO exposure sufficient to produce COHb levels of ca. 5% would be sufficient to produce visual sensitivity reduction and various neurobehavioral performance deficits. In a recent literature re-evaluation, however, the best estimate was that (COHb) would have to rise to 15–20% before a 10% reduction in any behavioral or visual measurement could be observed

(U.S.EPA, 1991). This conclusion was based on: critical review of the literature on behavioral and sensory effects, review and interpretation of the physiological effects of COHb on the CNS, extrapolation from the effects of hypoxic hypoxia to the effects of CO hypoxia, and extrapolation from rat behavioral effects of CO to humans.

In controlled human studies involving patients with documented coronary artery disease, mean postexposure COHb levels of 2.9–5.9% (corresponding to postexercise COHb levels of 2.0–5.2%) have been associated with a significant shortening in the time to onset of angina, with increased electrocardiographic changes and with impaired left ventricular function during exercise. In addition, ventricular arrhythmias may be increased significantly at the higher range of mean postexercise COHb levels (Hinderliter, 1989). Epidemiological and clinical data indicate that carbon monoxide from recent smoking and environmental or occupational exposures may contribute to cardiovascular mortality and the early course of myocardial infarction (Jetter, 2002). According to one study there has been a 35% excess risk of death from arteriosclerotic heart disease among smoking and nonsmoking tunnel officers, in whom the long-term mean COHb levels were generally less than 5% (Leichter, 1993). Current data from epidemiological studies and experimental animal studies indicate that common environmental exposures to carbon monoxide do not have atherogenic effects on humans (Jetter, 2002).

During pregnancy, endogenous production of carbon monoxide is increased so that maternal COHb levels are usually about 20% higher than the non-pregnant values. At steady state, fetal COHb levels are up to 10–15% higher than maternal COHb levels (Jetter, 2002). There is a well established and probably causal relationship between maternal smoking and low birth weight at fetal COHb levels of 2–10%. In addition, maternal smoking seems to be associated with a dose-dependent increase in perinatal deaths and with behavioural effects in infants and young children.

A synthesis of adverse health effects of CO exposure is presented in Table 1.

CO) in atmosphere		**(COHb)**	**Signs and symptoms**	
ppm	**mg/m**	**%**	**Healthy adults**	**Susceptible subpopulations**
0	0	0.4 – 0.7	Physiologic background concentration	
10	11.5	2	Asymptomatic	
17	19.5	2,9		during physical exertion reduced time to onset of angina and electrocardiogram signs of myocardial ischaemia in sunjects with coronary artery disease
		5-6	Decreases in work capacity and decrements of neurobehavioral function	Increase in cardiac arrythmias in subjects with coronary artery disease
42	48	7		Headache, nausea in children
		3-8	Background concentration in smokers	
70	80	10	No appreciable effect, except shortness of breath on vigorous exertion; possible tightness across the forehead; dilation of cutaneous blood vessels.	
		13		Cognitive development deficits in children

		15		Myocardial infarction in subjects with coronary artery disease
120	137	20	Shortness of breath on moderate exertion; occasional headache with throbbing in temples	
		25		syncopes in children – stillbirths
220	252	30	Decided headache; irritable; easily fatigued; judgment disturbed; possible dizziness; dimness of vision	
350-520	401-595	40-50	Headache, confusion; collapse; fainting on exertion	
800-1220	916-1400	60-70	Unconsciousness; intermittent convulsion; respiratory failure, death if exposure is long continued	
1950	2230	80	Rapidly fatal	

Table 1 - Carboxyhaemoglobin levels resulting from steady-state exposure to increasing concentrations of CO in ambient air and associated symptoms in healthy adult humans and susceptible (adapted from U.S.EPA, 2000; Ellenhorn and Barceloux, 1988)

Effects of long-term CO exposure

There is not enough reliable information on effects of chronic exposures to low concentrations from either controlled human studies, ambient population-exposure studies, or from occupational studies (Jetter, 2002). Chronic exposures to low CO concentrations may not pose as much a problem as high, acute exposure due to physiological compensation, tolerance, or adaptation.

CO emission sources and exposure levels

The most common cause of high carboxyhaemoglobin concentrations in man is the smoking of tobacco and the inhalation of the products by the smoker. Faulty domestic cooking and heating appliances, inadequately vented to outside air, may cause high indoor concentrations of CO. Also gas stoves, water heaters, and exhaust from vehicles in attached garages might be important indoor sources.

The most important source of carbon monoxide in ambient air is the exhaust of gasoline-powered motor vehicles. The emission rate depends on the type of vehicle, its speed, and its mode of operation.

Other common ambient sources include heat and power generators, especially when using coal, industrial processes such as the carbonisation of fuel, and the incineration of refuse (WHO, 1999).

Gaseous pollutants

Gaseous pollutants, other than carbon monoxide, that could affect cardiovascular system are ozone, nitric dioxide and sulphur dioxide.

Nitrogen dioxide (NO2) is a reddish brown gas with a characteristic pungent odour. Nitric oxide spontaneously produces the dioxide when exposed to air. Nitrogen dioxide gas is a strong oxidant, and reacts with water to produce nitric acid and nitric oxide. Significant human exposure to NO2 can occur in non-occupational indoor settings (Marbury, 1998 Spengler, 1994). Gas-burning appliances, such as unvented furnaces and stoves, are the principal sources of

indoor NOX, although kerosene space heaters and tobacco smoke may also play a role. (Borland, 1987). In urban areas, infiltration of ambient NO2 from vehicular emissions may also influence indoor exposures.
Epidemiological evidences of cardiovascular effects of NO2 exposure proceed form studies on outdoor air pollution. Moreover, it is very difficult to differentiate the effects of nitrogen dioxide from those of other pollutants in epidemiological studies.
Short-term effects of NO2 exposure have been investigated in time-series studies on mortality and morbidity in Europe and North America (Katsouyanni, 1996; Touloumi, 1997; Samoli, 2003; Atkinson, 1999; D'ippoliti, 2003; Samet, 2000; Burnett, 1997; Schwartz, 1997. Morris, 1995; Wong, 1999; Mann, 2002; Wellenius, 2005; Peters, 2000; Rich, 2005). These studies suggest that daily concentrations of nitrogen dioxide are significantly associated with increased cardiovascular mortality. Moreover, the results of time series include an increase in mortality for cardiovascular disease, and in hospital admissions for heart failure, arrhythmia and ischemic heart disease. Controlling for other pollutants at times lowers the effect estimates and at others makes them not statistically significant, and this makes the conclusions less clear. To date, no cardiovascular long-term effect of NO2 have been demonstrated.

Sulfure dioxide (SO2) is a colourless gas that is readily soluble in water. Sulfur dioxide is derived from the combustion of sulfur-containing fossil fuels. In nonoccupational settings, SO2 is generally found at substantially lower concentrations indoors than outside; however, the use of kerosene space heaters can generate significant indoor concentrations.
Literature about cardiovascular effects of SO2 is poor, and it prevalently include studies on outdoor air pollution health effects. A review of literature on Health effects of outdoor air pollution in developing countries in Asia (WHO, 2004) is suggestive for a positive association between SO2 levels and hospital admission for cardiovascular disease, in studies from Hong Kong. The European APHEA 2 project single pollutant models resulted in positive and significant sulfur dioxide risk estimates for all of the cardiac outcomes except stroke. However, these estimates were reduced when carbon monoxide, nitrogen dioxide, black smoke or PM10 were included in the model. The authors noted that sulfur dioxide could be a surrogate of urban pollution mixtures that in some cases is more strongly associated with cardiovascular hospital admissions than particles (La Tertre, 2002-2003; Sunyer, 2003; Wong, 2002). In an analysis of morbidity after the step-change in ambient sulfur dioxide concentration in Hong Kong, Wong et al. (Wong, 1998) concluded that for sulfur dioxide concentrations in the 5–40-$\mu g/m^3$ range in Hong Kong, there were non-threshold and nearly linear relationships between sulfur dioxide on the one hand and cardiac admissions on the other, but no trends for ischemic heart disease.
Moreover, the influence of SO2 levels on PM10 risk estimates has been investigated in the U.S. NNMAP (re-analysis by Schwartz et al in 2003). The authors concluded that there was little evidence of PM10 effects confounded by sulfur dioxide.

Ozone (O3) and other photochemical oxidants are pollutants that are not directly emitted by primary sources. Rather, they encompass a group of chemical species formed through a series of complex reactions in the atmosphere driven by the energy transferred to nitrogen dioxide (NO2) molecules when they absorb light from solar radiation. In most buildings indoor ozone has been transported from outdoor. Indoor ozone concentrations track outdoor concentrations with a slight time lag that depends on the air exchange rate.
There is solid evidence that ozone acutely increases morbidity (WHO, 2005). To date, data about cardiovascular effects of ozone exposure are poor also because in studies of acute responses to pollutants in humans it is generally not possible to separate effects due to peaks in PM concentrations from those that may be due to ozone. In a review presented in the Air Quality Guidelines of WHO – Europe 2005, 10 of the 15 reviewed studies, focusing on cardiovascular

diseases, showed no significant effects of ozone. In addition, there is no clear positive effect of ozone on any of the particular end-points evaluated (myocardial infarction, sudden death, stroke, congestive heart failure and peripheral arterial diseases).
Thus, on the basis of the available information, it is clear that the effects of ozone on cardiovascular morbidity need further evaluation (WHO, 2005). However a recent analysis of the link between ambient air pollution and the risk of hospital cardiac readmissions of MI survivors suggests that the strength of associations with same-day CO, O_3, or NO_2 was similar to that for PM_{10} (von Klot, 2005) suggesting a significant contribution of ozone among gaseous co-pollutants.

Identification of susceptible population subgroups
People who already have heart disease are at especially high risk of acute events, if exposed to SHS.
At CO levels typically encountered in indoor and outdoor environments, health effects are most likely to occur in individuals who are physiologically stressed, either by exercise or by medical conditions that can make them more susceptible to low levels of CO. Subpopulations at increased risk of adverse effects are:
1. Individuals with cardiovascular diseases: COHb levels of 2-6% may impair the delivery of oxygen to the myocardium causing hypoxia and increasing coronary blood flow demand by nearly 30%. When myocardial oxygen demands are increased, as in exercise, the hypoxic effects of CO may exceed the limited coronary reserve producing adverse health effects including earlier onset of myocardial ischaemia, reduced exercise tolerance in persons with stable angina pectoris, increased number and complexity of arrhythmias, and increased hospital admissions for congestive heart failure.
2. Fetuses are more susceptible to CO exposure for several reasons: CO crosses the placenta; fetal Hb has greater affinity for CO than maternal Hb; the half-life of COHb in fetal blood is three times longer than that of maternal blood, and the fetus has high rate of oxygen consumption and lower oxygen tension in the blood than adults. Also, maternal smoking during pregnancy exposes the fetus to greater than normal concentrations of CO leading to a decrease in birth weight.
3. Children develop acute neurotoxic effects (e.g. headaches, nausea), long-lasting neurotoxic effects (e.g. memory deficits) and impaired ability to escape (i.e. syncopes) at lower (COHb) than adults. Children have greater activity levels and smaller body masses than adults and should therefore experience higher levels of CO uptake than will adults for the same average exposure concentration.
4. Pregnant women have increased alveolar ventilation, increasing the rate of CO uptake from inspired air. Also, a pregnant woman produces nearly twice as much endogenous CO.
5. Individuals with chronic obstructive pulmonary disease such as chronic bronchitis, emphysema and chronic obstructive pulmonary disease are more susceptible to CO effects, since their lungs are less efficient at oxygenating the blood.
6. Individuals with reduced blood haemoglobin concentrations, or with abnormal haemoglobin, will have reduced O2 carrying capacity in blood. In addition, disease processes that result in increased destruction of red blood cells (haemolysis) and accelerated breakdown of haemoproteins accelerate endogenous production of CO, resulting in higher COHb concentrations than in normal individuals. For example, patients with haemolytic anemia have COHb concentrations 2 to 3 times those seen in normal individuals.
7. Certain occupational groups are at risk from ambient CO exposure including those who work on city streets (street repairmen, street cleaners, street vendors, deliverymen, and garage attendants, taxi and bus drivers). Individuals who work in industrial processes including those

exposed to other chemical substances (e.g. methylene chloride) that increase endogenous CO formation.
8. Individuals who have not adapted to high altitude and are exposed to a combination of high altitude and CO.

As to short-term and long-term air pollution (including PM and gaseous pollutants) exposures related to cardiovascular diseases, whether there are specific individuals or subsets of patients at increased relative risk is less well documented. Some observations have suggested that people suffering from cardiovascular diseases are more vulnerable to particles and NO2 and persons suffering from asthma and other respiratory diseases are more susceptible to particles. Moreover, the elderly and those with less than a high school education (low socioeconomic status) may be particularly susceptible populations. According to a few recent studies women gender seems to be more prone to cardiovascular effects of PM than men.

Conclusions

Environmental cardiology is a emerging field of research. The identification of modifiable risk factors for cardiovascular disease such as smoking and diet, supports the perception that the environment significantly influences cardiovascular health. The indoor environment represents an important microenvironment in which people spend a large part of their time each day, so that exposure to cardio-toxic indoor air pollutants could have a role in the cardiovascular etiopathology.

Assessment of the policy relevance of literature data

PM

Evidence is emerging that exposure to low concentration of PM is associated with cardiovascular mortality.
During the past 15 years, a number of studies identified a link between short term PM exposure and overall cardiovascular mortality. Direct associations have also been identified with respect to incidence of ischemic heart disease, arrhythmias, and heart failure. Elevations in air pollution have also been associated with increased blood pressure. Long-term exposure to PM have been demonstrated to be independently related to cardiovascular mortality in general and in particular to mortality for ischemic heart disease, arrhythmia, heart failure and cardiac arrest.
To date, there have been only a limited number of studies on the association of measures of ultrafine particles with risk of cardiovascular effects.
Current evidences suggest a possible link between exposure to indoor PM and cardiovascular diseases onset, however more research is needed. Also there is a need to identify the role of the ultrafine fraction.

Secondhand smoke

Many reviews have been published summarizing the epidemiological studies about the association between SHS and increase risk for CVD.

Carbon monoxide

At CO levels typically encountered in indoor environments, health effects are most likely to occur in individuals who are physiologically stressed, either by exercise or by medical conditions that can make them more susceptible to low levels of CO. Subpopulations at increased risk of adverse effects include: individuals with cardiovascular diseases, pregnant women also with respect to fetal exposure, children, subjects with chronic obstructive pulmonary disease, individuals with reduced blood haemoglobin concentrations.

Gaseous pollutants

Epidemiological evidences of cardiovascular effects of NO2 exposure proceed form studies on outdoor air pollution. Moreover, it is very difficult to differentiate the effects of nitrogen dioxide from those of other pollutants in epidemiological studies.

Literature about cardiovascular effects of SO2 is poor, and it prevalently include studies on outdoor air pollution health effects.

To date, data about cardiovascular effects of ozone exposure are poor. Thus, on the basis of the available information, it is clear that the effects of gaseous pollutants on cardiovascular morbidity need further evaluation and no clear conclusions can be made.

Assessment of the relevance of indoor exposure threshold levels

PM

As to PM, exposure threshold levels are not yet specifically stated for indoor air. The American Society of Heating, Refrigerating, and Air-conditioning Engineers (ASHRAE) has adopted, for indoor air, the outdoor limits of the US-Environmental Protection Agency - National Ambient Air Quality Standards (US-EPA-NAAQS), as concern PM10 (150 $\mu g/m^3$/24h). This value is higher than the corresponding limit for outdoor air quality reported by WHO, that is 50 $\mu g/m^3$/24 h. There are no indoor standards for PM2.5. WHO suggests, for outdoors, 25 $\mu g/m^3$/24 h and 10 $\mu g/m^3$/1 year respectively.

Secondhand smoke

The adverse effects of exposure to environmental tobacco smoking (ETS) are well established ETS exposure occurs in private households, work and public places. Several countries have enacted legislation that prohibits smoking in work and public places, but the interest towards policies to address exposure in households is more limited.

Carbon monoxide

On the basis of human clinical data, to protect non smoking, middle-aged and elderly population groups with documented or latent coronary artery disease from acute ischaemic heart attacks and to protect the fetuses of non-smoking pregnant women from untoward hypoxic effects, a COHb level of 2.5% shoul not be exceeded. not to exceed a COHb level of 2.5% the following guideline values and period of time-weghted average exposures have been determined:

100 mg/m^3 (90 ppm) for 15 min
60 mg/m^3 (50 ppm) for 30 min
30 mg/m^3 (25 ppm) for 1 hour
10 mg/m^3 (10 ppm) for 8 hours

The US EPA's National Ambient Air Quality Standard (NAAQS) is again 10 mg/m^3 for an 8-hour average.

Gaseous pollutants

As to nitrogen dioxide a 1-hour guideline of 200 $\mu g/m^3$ is proposed (WHO).

As to ozone, the fisrt edistion of Air Quality Guidelines for Europe recommended a 1-hour guideline value of 150-200 $\mu g/m^3$.

Control options

In order to decrease indoor air pollution, measures can be implemented with various types of actions. These include mandatory and voluntary actions on international or national level.

Building codes and standards

As the buildings represent the largest share of property values in Europe it is natural that the quality of buildings are controlled with European and national building codes and standards. For the construction industry the common European standards would be beneficial. Of course the climatic and cultural differences should be considered in the standards and guidelines.

Prenormative work (ALA 2001, ASHRAE 62, ASHRAE GPC10 2001, Björck 2002, Canadian standard Z204-1994, CIB 2002, ISO 2002, CEN TC 156 2002, HB 2000, Jonsen et al. 1996, Samuelsson 2000, Tuomainen 2002) done by research institutes, construction companies and professional organisations is important in this area. Building codes and standards are needed specially:
- *to improve ventilation and*
- *to control moisture in buildings.*

Consumer information

A way to implement the measures is based on voluntary actions with education and information campaigns. The patient associations like the member societies of European Federation of Allergy and Airways Diseases Patients´ Association have an important role in implementing this type of campaigns, however, the campaigns should be implemented in co-operation with professional organisations and with government support. Good experience of this type of successful campaigns is the Finnish Asthma Programme (Asthma Programme in Finland 1994-2004). The programme has been effective. Mortality and days of hospitalisation have decreased even though percentage of asthmatic persons has increased to four fold during the last twenty years (Haahtela et al. 2001). Shorter campaigns like Swedish Indoor Climate Year 1999 and Finnish Indoor Climate Information and Education Year 2002 (Seppänen 2003b) have also been effective. Some efforts have also been done on the international level (Nato). The campaigns should focus, but not limit to the following actions:
- *to limit the exposure to environmental tobacco smoke*
- *to improving cleaning and housing hygiene*
- *to avoid the use of carpets and other harmful materials*

PM

As to indoor generated particulate matter, measures include the control of the source, improvement of ventilation, better cleaning and housing hygiene and avoiding of carpets. The use of vacuum cleaners and central vacuum cleaning systems should be encouraged, along with the development of performance criteria for vacuum cleaners, the cleaning after or before the operation hours of the schools and offices should be encouraged.

Carbon monoxide

As to CO, the main measure to be adopted to reduce CO levels is controlling the source of exposure. Management options include: connecting each combustion equipment/appliance to chimney or vented hood, ensuring sufficient local extract ventilation in kitchens with gas stove, mandatory inspection and maintenance of indoor combustion devices, and CO alarms.
Following general recommendations are also suggested:
• Restrict tobacco smoking in all indoor spaces;
• Restrict the construction of attached garages, or isolate them from living and working spaces;
• Ensure that ventilation dilutes predictable indoor emissions below the guideline levels;
• Raise public awareness about indoor air risks.

Gaseous pollutants

As to NOx, preventives measures to be adopted include the control of the source, improvement of ventilation; the use of electrical kitchen appliances should be encouraged, while the use of unvented heating appliances should be avoided.

References

Atkinson, R.W., et al., Short-term associations between emergency hospital admissions for respiratory and cardiovascular disease and outdoor air pollution in London. Arch Environ Health, 1999. 54(6): p. 398-411.

Barnett, A.G., et al., The effects of air pollution on hospitalizations for cardiovascular disease in elderly people in Australian and New Zealand cities. Environ Health Perspect, 2006. 114(7): p. 1018-23.

Bhatnagar, A., Cardiovascular pathophysiology of environmental pollutants. Am J Physiol Heart Circ Physiol, 2004. 286(2): p. H479-85.

Bhatnagar, A., Environmental cardiology: studying mechanistic links between pollution and heart disease. Circ Res, 2006. 99(7): p. 692-705.

Borland, C. and T. Higenbottam, Nitric oxide yields of contemporary UK, US and French cigarettes. Int J Epidemiol, 1987. 16(1): p. 31-4.

Brook, R.D., et al., Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation, 2004. 109(21): p. 2655-71.

Brunekreef, B. and S.T. Holgate, Air pollution and health. Lancet, 2002. 360(9341): p. 1233-42.

Burnett, R.T., et al., Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. Arch Environ Health, 1999. 54(2): p. 130-9.

Burnett, R.T., et al., The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. Environ Health Perspect, 1997. 105(6): p. 614-20.

Chen, L.H., et al., The association between fatal coronary heart disease and ambient particulate air pollution: Are females at greater risk? Environ Health Perspect, 2005. 113(12): p. 1723-9.

Dahms TE, Younis LT, Wiens RD, Zarnegar S, Byers SL, & Chaitman BR Effects of carbon monoxide exposure in patients with documented cardiac arrhythmias. J Am Coll Cardiol, 1993; 21(2): 442-450.

de Hartog, J.J., et al., Effects of fine and ultrafine particles on cardiorespiratory symptoms in elderly subjects with coronary heart disease: the ULTRA study. Am J Epidemiol, 2003. 157(7): p. 613-23.

D'Ippoliti, D., et al., Air pollution and myocardial infarction in Rome: a case-crossover analysis. Epidemiology, 2003. 14(5): p. 528-35.

Dockery, D.W., et al., An association between air pollution and mortality in six U.S. cities. N Engl J Med, 1993. 329(24): p. 1753-9.

Dominici, F., et al., Airborne particulate matter and mortality: timescale effects in four US cities. Am J Epidemiol, 2003. 157(12): p. 1055-65.

Dominici, F., et al., Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA, 2006. 295(10): p. 1127-34.

Effects of passive smoking on health. Report of the NHMRC Working Party on the effects of passive smoking on health. , C.A.G.P. Service, Editor. 1997.

Ellenhorn MJ & Barceloux DG ed 1988 Medical toxicology diagnosis and treatment of human poisoning. New York, Elsenin, pp 820-829.

European cardiovascular disease statistics 2005 edition http://www.heartstats.org/uploads/documents%5CPDF.pdf

Forastiere, F., et al., Socioeconomic status, particulate air pollution, and daily mortality: differential exposure or differential susceptibility. Am J Ind Med, 2007. 50(3): p. 208-16.

Franklin, M., A. Zeka, and J. Schwartz, Association between PM2.5 and all-cause and specific-cause mortality in 27 US communities. J Expo Sci Environ Epidemiol, 2007. 17(3): p. 279-87.

Goldberg, M.S., et al., Identification of persons with cardiorespiratory conditions who are at risk of dying from the acute effects of ambient air particles. Environ Health Perspect, 2001. 109 Suppl 4: p. 487-94.

Greenland, P., et al., Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA, 2003. 290(7): p. 891-7.

Grundy, S.M., et al., Primary prevention of coronary heart disease: guidance from Framingham: a statement for healthcare professionals from the AHA Task Force on Risk Reduction. American Heart Association. Circulation, 1998. 97(18): p. 1876-87

Hanninen, O., et al., Response to findings on association between temperature and dose response coefficient of inhalable particles (PM10). J Epidemiol Community Health, 2007. 61(9): p. 838.

Health aspects of air pollution with particulate matter, ozone, and nitrogen dioxide. Report on a WHO working group. 2003, WHO Regional Office for Europe: Copenhagen.

Health aspects of air pollution. Results from the WHO project “Systematic review of health aspect of air pollution in Europe”. 2004, WHO Regional Office for Europe: Copenhagen.

Health Effects of Exposure to Environmental Tobacco Smoke: Final Report. 1999, Californian Environmental Protection Agency.

Heller, R.F., et al., How well can we predict coronary heart disease? Findings in the United Kingdom Heart Disease Prevention Project. Br Med J (Clin Res Ed), 1984. 288(6428): p. 1409-11.

Henneberger, A., et al., Repolarization changes induced by air pollution in ischemic heart disease patients. Environ Health Perspect, 2005. 113(4): p. 440-6.

Hennekens, C.H., Increasing burden of cardiovascular disease: current knowledge and future directions for research on risk factors. Circulation, 1998. 97(11): p. 1095-102.

Hinderliter AL, Adams KF Jr, Price CJ, Herbst MC, Koch G, & Sheps DS. Effects of low-level carbon monoxide exposure on resting and exerciseinduced ventricular arrhythmias in patients with coronary artery disease and no baseline ectopy. Arch Environ Health 1989; 44: 89-93.

Hoek, G., et al., The association between air pollution and heart failure, arrhythmia, embolism, thrombosis, and other cardiovascular causes of death in a time series study. Epidemiology, 2001. 12(3): p. 355-7.

Hong, Y.C., et al., Air pollution: a new risk factor in ischemic stroke mortality. Stroke, 2002. 33(9): p. 2165-9.

Ibald-Mulli, A., et al., Effects of air pollution on blood pressure: a population-based approach. Am J Public Health, 2001. 91(4): p. 571-7.

ISTAT, Istituto nazionale di statistica, Italy

Institut de veille sanitaire, France, personnal communication

Jetter J, Guo Z, Jenia, McBrian JA, Flynn MR. Characterization of emissions from burning incense. The Science of The Total Environment 2002; 295: 51- 67.

Kannel, W.B., Contributions of the Framingham Study to the conquest of coronary artery disease. Am J Cardiol, 1988. 62(16): p. 1109-12.

Katsouyanni, K., et al., Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. Epidemiology, 2001. 12(5): p. 521-31.

Katsouyanni, K., et al., Short term effects of air pollution on health: a European approach using epidemiologic time series data: the APHEA protocol. J Epidemiol Community Health, 1996. 50 Suppl 1: p. S12-8.

Kettunen, J., et al., Associations of fine and ultrafine particulate air pollution with stroke mortality in an area of low air pollution levels. Stroke, 2007. 38(3): p. 918-22.

Khot, U.N., et al., Prevalence of conventional risk factors in patients with coronary heart disease. JAMA, 2003. 290(7): p. 898-904.

Law, M.R., J.K. Morris, and N.J. Wald, Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. BMJ, 1997. 315(7114): p. 973-80.

Le Tertre, A., et al., Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. J Epidemiol Community Health, 2002. 56(10): p. 773-9.

Le Tertre, A., Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. , in Revised analyses of timeseries studies of air pollution and health. Special report. , M. Boston, Health Effects Institute, Editor. 2003. p. 173-176.

Leichter, J. 1993. Fetal growth retardation due to exposure of pregnant rats to carbon monoxide. Biochem. Arch. 9:267-272.

Levi, F., et al., Trends in mortality from cardiovascular and cerebrovascular diseases in Europe and other areas of the world. Heart, 2002. 88(2): p. 119-24.

Mann JK, Tager IB, Lurmann F, Segal M, Quesenberry CP Jr, Lugg MM, Shan J, Van Den Eeden SK. Air pollution and hospital admissions for ischemic heart disease in persons with congestive heart failure or arrhythmia. Environ Health Perspect 2002; 110(12):1247-52.

Mann, J.K., et al., Air pollution and hospital admissions for ischemic heart disease in persons with congestive heart failure or arrhythmia. Environ Health Perspect, 2002. 110(12): p. 1247-52.

Marbury, M.C., et al., Indoor residential NO2 concentrations in Albuquerque, New Mexico. JAPCA, 1988. 38(4): p. 392-8.

Morris, R.D., E.N. Naumova, and R.L. Munasinghe, Ambient air pollution and hospitalization for congestive heart failure among elderly people in seven large US cities. Am J Public Health, 1995. 85(10): p. 1361-5.

National Toxicology Program. 11th Report on Carcinogens, 2005. . 2000, Research Triangle Park, NC: U.S. Department of Health and Human Sciences, National Institute of Environmental Health Sciences.

Pekkanen, J., et al., Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease: the Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study. Circulation, 2002. 106(8): p. 933-8.

Peters, A., et al., Air pollution and incidence of cardiac arrhythmia. Epidemiology, 2000. 11(1): p. 11-7.

Peters, A., et al., Exposure to traffic and the onset of myocardial infarction. N Engl J Med, 2004. 351(17): p. 1721-30.

Poloniecki, J.D., et al., Daily time series for cardiovascular hospital admissions and previous day's air pollution in London, UK. Occup Environ Med, 1997. 54(8): p. 535-40.

Pope, C.A., 3rd, Epidemiology of fine particulate air pollution and human health: biologic mechanisms and who's at risk? Environ Health Perspect, 2000. 108 Suppl 4: p. 713-23.

Pope, C.A., 3rd, et al., Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation, 2004. 109(1): p. 71-7.

Pope, C.A., 3rd, et al., Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA, 2002. 287(9): p. 1132-41.

Research priorities for airborne particulate matter. IV. Continuing research progress. , D. Washington, National Academies Press, Editor. 2004, National Research Council.

Rich, D.Q., et al., Association of short-term ambient air pollution concentrations and ventricular arrhythmias. Am J Epidemiol, 2005. 161(12): p. 1123-32.

Ritz, B. and Yu,F. The effect of ambient carbon monoxide on low birth weight among children born in southern California between 1989 and 1993. Environ Health Perspect 1999; 107:17-25.

Samet, J.M., et al., The National Morbidity, Mortality, and Air Pollution Study. Part II: Morbidity and mortality from air pollution in the United States. Res Rep Health Eff Inst, 2000. 94(Pt 2): p. 5-70; discussion 71-9.

Samoli, E., et al., Investigating the dose-response relation between air pollution and total mortality in the APHEA-2 multicity project. Occup Environ Med, 2003. 60(12): p. 977-82.

Sarwar, G., et al., Indoor fine particles: the role of terpene emissions from consumer products. J Air Waste Manag Assoc, 2004. 54(3): p. 367-77.

Schwartz, J., Air pollution and hospital admissions for cardiovascular disease in Tucson. Epidemiology, 1997. 8(4): p. 371-7.

Schwartz, J., Air pollution and hospital admissions for heart disease in eight U.S. counties. Epidemiology, 1999. 10(1): p. 17-22.

Schwartz, J., Morbidity and mortality among elderly residents of cities with daily PM measurements in Revised analyses of timeseries studies of air pollution and health. Special report. , M. Boston, Health Effects Institute, Editor. 2003. p. 25-58.

Sheps DS, Herbst MC, Hinderliter AL, Adams KF, Ekelund LG, O'Neil JJ, Goldstein GM, Bromberg PA, Dalton JL, Ballenger MN, Davis SM, & Koch GG. Production of arrhythmias by elevated carboxyhemoglobin in patients with coronary artery disease. Ann Intern Med, 1990 113: 343-351.

Spengler, J., et al., Personal exposure to nitrogen dioxide in the Los Angeles Basin. Air Waste, 1994. 44(1): p. 39-47.

Sunyer, J., et al., The association of daily sulfur dioxide air pollution levels with hospital admissions for cardiovascular diseases in Europe (The Aphea-II study). Eur Heart J, 2003. 24(8): p. 752-60.

Surgeon General's report highlights the health impact of smoking among women. Clin J Oncol Nurs, 2001. 5(5): p. 189.

Touloumi, G., et al., Short-term effects of ambient oxidant exposure on mortality: a combined analysis within the APHEA project. Air Pollution and Health: a European Approach. Am J Epidemiol, 1997. 146(2): p. 177-85.

Tsai, S.S., et al., Evidence for an association between air pollution and daily stroke admissions in Kaohsiung, Taiwan. Stroke, 2003. 34(11): p. 2612-6.

U.S. 2006 Surgeon General's Report: The Health Consequences of Involuntary Exposure to Tobacco Smoke. 2006, U.S. 2006 Surgeon General's Report

U.S.EPA. Air quality criteria for carbon monoxide. EPA 600/P-99/001F, U. S. Environmental Protection Agency, Office of Research and Development, Washington, D.C., 2000.

U.S.EPA. Air quality criteria for carbon monoxide. Washington, DC. US Environmental Protection Agency, Office of Research and Development, 1991 publication no. EPA-600/B-90/045F, 1991.

von Klot, S., et al., Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in five European cities. Circulation, 2005. 112(20): p. 3073-9.

Wainman, T., et al., Ozone and limonene in indoor air: a source of submicron particle exposure. Environ Health Perspect, 2000. 108(12): p. 1139-45.

Wellenius, G.A., et al., Particulate air pollution and the rate of hospitalization for congestive heart failure among medicare beneficiaries in Pittsburgh, Pennsylvania. Am J Epidemiol, 2005. 161(11): p. 1030-6.

Weschler, C.J., Ozone in indoor environments: concentration and chemistry. Indoor Air, 2000. 10(4): p. 269-88.

WHO Air Quality Guidelines (AQG) for Europe. 2005, WHO - Regional Office for Europe.

WHO. Environmental Health Criteria 213, Carbon Monoxide Second Edition, IPCS, International Programme on Chemical Safety; World Health Organization, Geneva, Switzerland, 1999.

Wichmann, H.E., et al., Daily mortality and fine and ultrafine particles in Erfurt, Germany part I: role of particle number and particle mass. Res Rep Health Eff Inst, 2000(98): p. 5-86; discussion 87-94.

Wolkoff, P., et al., Organic compounds in office environments - sensory irritation, odor, measurements and the role of reactive chemistry. Indoor Air, 2006. 16(1): p. 7-19.

Wong, C.M., et al., A tale of two cities: effects of air pollution on hospital admissions in Hong Kong and London compared. Environ Health Perspect, 2002. 110(1): p. 67-77.

Wong, C.M., et al., Comparison between two districts of the effects of an air pollution intervention on bronchial responsiveness in primary school children in Hong Kong. J Epidemiol Community Health, 1998. 52(9): p. 571-8.

Wong, T.W., et al., Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. Occup Environ Med, 1999. 56(10): p. 679-83.

Worth, R.M., et al., Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: mortality. Am J Epidemiol, 1975. 102(6): p. 481-90.

Odour and irritations (sbs symptoms)

Lars Mølhave

Department of Occupational and Environmental Medicine, The Institute of Public health, The University of Aarhus. Vennelyst Boulevard 6, DK8000, Aarhus, Denmark.

Introduction

Health is a state of complete physical, mental and social well-being and not merely the absence of decease or infirmity (WHO 1948). Therefore, the health effects of interest indoors include both adverse effects and changes of well-being. Building-Related Illness (BRI) is a group of such health effects with known causality between symptoms and indoor exposures to air pollutants. Generally, these causalities show a uniform clinical picture and a specific cause of the complaints. Many of the BRIs are manifestations at relatively low exposure levels of adverse effects known from high e.g. occupational exposures. The symptomatology is therefore important for diagnoses of adverse effects at long time low exposure levels indoors. Therefore, the prevalence of building-related symptoms (BRI) is commonly used to characterize the indoor air quality (IAQ) in office buildings (Niemela et al 2006). An association may exist between BRI and productivity or sick leave (Niemela et al 2006).

The term objective health effects is used for quantifiable changes or signs observed by an independent observer (not the exposed person). In contrast, symptoms and perceptions are personal experiences or judgements made by the exposed occupant. Often, symptoms are unspecific i.e. many exposures may cause each of them. Therefore they do not alone identify the exposure cause. For each symptom multiple response modifiers and multiple biases are possible and different persons may have different spectrum and intensity of symptoms. Also, most indoor exposures may cause a number of different signs and symptoms. Therefore, objective measurements of effects are preferred and subjective ratings should be substituted by objective measurements where possible but unfortunately few are available. On the other hand, objective measurements are expensive and time consuming, a fact which in many cases prevent their use and in the absence of instrumentation for chemical detection of small amounts of some air pollutants, the senses remain the most sensitive indicator system (Berglund et al 1992). Added to this is that discomfort is subjective by nature and cannot be measured without subjective evaluations. Many symptoms are therefore important per se, and cannot be substituted by objective measurements.

Aims

This chapter aim at both an update on the biological background for known symptoms and perceptions in IAQ science and practice as well as presenting some of the newest literature in the field. The paper discusses how subjective evaluations can be substituted by objective measurements, and if IAQ guidelines can be defined for signs and subjective symptoms. Finally, recommendations are given on guideline settings for IAQ. This review includes literature younger than a review made by Berglund et al (1992). It does not pretend to be complete but merely summarizes uses of symptoms and perceptions during the last 5-7 years in IAQ research and managements of buildings. The focus is on symptoms and subjective ratings, not on objective health effects.

Brief description of symptoms and perceptions and their causes

Indoor airborne exposure of humans to indoor pollutants may either affect sensory systems or result in tissue changes. Table 1 summarises some of the biological reactions or processes which may be active in human responses to poor IAQ.

The chemical sense

The chemical senses include specialised receptors for odours and irritants in eyes, facial skin and nose cavity. These senses incorporate n. Olfactorius (odours) and n.Trigeminus (irritants). Most odorous compounds are also irritants and visa versa and the chemical sense acts as a warning system (Berglund et al 1992). Mixtures of pollutants may interact and one odorant may mask other odorants (e.g. Pan et al 2000). The time course of effects may show adaptation or accumulation of effects which create problems for the interpretation of causality behind activation of the chemical sense.

Unspecific pain and irritative receptors

Unspecific pain and irritative receptors in the skin or mucosa of eye, nose, throat, and air ways are other sensory systems active in response to indoor air pollution (IAP). These senses detect the status of the tissues including presence of absorbed irritants or initiate release of irritating signalling compounds or reflexes in the exposed tissue.

Visual observations

Visual observations are involved in observations of skin rashes, smog, or dust in the air and thus influence the subjective evaluation of the effects of poor IAQ.

Immunological responses

Immunological responses to Indoor Air Pollution (IAP) include such diseases as allergic asthma and extrinsic allergic alveolitis (hypersensitivity pneumonitis) which are the two most serious allergic diseases caused by allergens in indoor air. Allergic rhinoconjunctivitis and humidifier fever are other important diseases. The biological mechanisms include immunological specific IgE sensitisation to an airborne allergen. The type of symptoms observed in allergic asthma is characterised by reversible narrowing of the lower airways leading to difficulties in breathing, tightness of breath, respiratory sounds etc. Other symptoms are itching of the eye and/or the nose, sneezing, watery nasal secretion and some stuffiness of the nose. Pulmonary function during an attack shows an obstructive pattern in serious cases together with reduced respiratory ventilation capacity. Many objective measurements are available but may not apply at low indoor exposure levels where the symptomatology becomes more important.

Inflammation

Two types of sensory irritation appear in the literature to be related to 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 (Berglund et al 1992). Each of these may subsequently lead to the other. Often inflammation is a direct effect of chemicals on the tissue cells leading to cell damages. Through release of mediating compounds, the cells may signal the need of activation of defensive responses. 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. Non-allergic asthma-type of responses may be related to inflammatory responses. 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. Irritative effects causing tissue changes in the skin and mucous membranes have been reported in many forms, although they have seldom been seen in an adverse form to follow exposure to normal indoor air (Berglund et al 1992).

The body's signalling systems

Body signalling systems may be activated by biomarkers or neural activity. These reactions follow both from immune and inflammatory responses and include biomarker or mediator compounds released in the tissues and neural activity in the form of reflexes. Both are signalling the status of the body and initiate defensive responses where needed. Immune responses or weak irritative reactions may lead to release of signalling compounds or biomarkers such as histamine or cytokines. These compounds may by themselves be irritative in the tissue and may thus accelerate the irritative effects. These responses may be observed as rashes, skin reddening etc. Neural reflexes are often defensive reactions. The symptoms are related to watering eyes, secretion of mucosa or tears, increased blood flow in the exposed tissues, bronchial constriction, or cilia movements in the upper airways, or cough. The effects may often but not always appear at the site of contact on the exposed skin or mucosa.

Central nervous system (CNS)

Symptoms or perceptions are reported as processed evaluations incorporating many symptoms or perceptions such as perceived comfort or air quality. It is not known how this is done in the Central Nervous System (CNS). They are typically reported by the occupant as prevalence or intensity of symptoms or perceptions. The reports are strongly affected by personal or external biases, and frequently adaptation and sensitization appear.

The two dimensions of symptoms and reports

Indoor air pollutants may each activate a multitude of biological mechanisms and subjects are often experiencing many exposures at the same time. Because of this and the complex nature of the resulting subjective reports as described above, no consistent and general agreed classification exists of reports of symptoms or evaluations of IAQ. Here a suggested classification is found in table 2 which shows three groups of perceptions, symptoms, well-being and other subjective health effects in relation to IAQ. The table is a modification of a classification suggested by (Berglund et al 1992). The three groups of symptoms and perceptions are here for simplicity called "Perceptions of body functions", "Environmental perceptions", and "Processed reports or evaluations". These classes are defined with consideration to whether they can be replaced by objective measurements or not or if the target value for their prevalence in guideline setting is zero or not.

Perceptions of body functioning

Perceptions of body functioning are reported symptoms of mal-functioning body systems, inside the body or on the body surface. These may be caused by immune or inflammatory reactions. Focus of occupants' reports are on the type of organs affected such as eyes, nose, mouth, or throat (exposed mucosa), skin, respiratory malfunction, allergic asthma responses, non-immune responses, bronchial constriction, CNS changes (e.g. reaction time and errors), and increased responsiveness (e.g. hyperreactivity, allergy). Many of the biological mechanisms mentioned above may at the same time be involved in each reported symptom. Typical symptoms are dryness, increased secretion, perceived irritation, soreness, cough, tightness of breath, headache,

rashes, stinging, itching, burning. Although biologically different, subjective reports of irritation of mucous membranes in eyes, nose, and throat caused by inflammatory or immunological responses cannot be separated from responses of the chemical sense n.Trigeminus. In principle, objective measurements can be used for most if not for all and objective measurements exist for many of the physiological effects reported by these body perceptions but not for all. These body perceptions are characterized by a target value for guideline settings and recommendations of zero prevalence.

Environmental perceptions

Environmental perceptions include perception of the environment including the presence of any air pollutants. Typical reports include odours as response to odorants in the air (n. Olfactorius) and irritation (n. Trigeminus and the chemical sense) in mucous membranes, nose and eyes, and facial skin (unspecific censors in the skin may be included). Other important IAQ senses relate to air temperature, humidity, and vision. The environmental senses also include hearing, taste, noise, draught, and illumination. These will not be dealt with in this summary. Adverse perceptions are unwanted changes of life quality and thus full-value health effects (Berglund et al 1992). However some levels of perceptions are required to allow persons to follow changes in the status of their environment. It follows that these perceptions may have a D-R relation of U-form i.e. in guideline settings the prevalence target is non-zero. The detection of ocular and nasal sensory irritation increases as a function of vapour concentration at much higher rate than that for the detection of odour. However the odour intensity of mixtures of odorants cannot presently be predicted (Cometto-Muniz et al 2004). Although biologically different, subjective reports of activation of the chemical sense and n.Trigeminus cannot be separated from responses caused by irritation of mucous membranes in eyes, nose, and throat following inflammatory or immunological reactions in the tissues. Recent work in this area is summarized above.

Processed evaluations and syndromes

The processed evaluations are based on multiple symptoms or perceptions. They are interpersonal dynamic interactions expressing the person’s emotional content of body and environmental perceptions.

Processed evaluations are important indicators of IAQ. By definition they are based on psychological processes and thus cannot be documented without using subjective reports. However, they are difficult to use in scientific research and in investigation of buildings with poor IAQ. They include many symptoms´ complexes such as syndromes (a spectrum of related symptoms) and overall evaluations of many symptoms combined into one evaluation. An example is the "Sick Building Syndrome" (SBS) in which the affected workers report non-specific symptoms only during the time at work, most often with no known cause (Berglund et al 1992). Symptoms reported in SBS have typically included mucous membrane and eye irritation, cough, chest tightness, fatigue, headache, and malaise. The criteria for the definition of SBS are summarised in Table 3. 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 (EU 1989, Berglund et al 1992). The use of SBS should be discouraged and replaced by multi-symptom questionnaires such as MM 40 (Lahtinen et al 2004). Other examples are “Perceived air quality” which is a mixture of odour, irritation, stuffiness, feeling of heavy head, stuffy or stale air resulting from stimulation of both the nerves Trigeminus and Olfactorius, “Comfort” or “Well-being” which seem to be a mixture of body symptoms or body perceptions. Discomfort and general well-being are in many investigations used as independent evaluations. “General Well-being” or “General Symptoms” in many publications seem to be a mixture of body symptoms or body perceptions, etc. Finally, productivity and absenteeism has been related to IAQ. Productivity and learning capacity are also integrating CNS changes.

The main indoor air pollutants and related sources causing the disease

The relevant IAPs are those which alone or in combination can stimulate our senses or cause tissue changes i.e. all known indoor airborne chemicals at some level (maybe excluding radon and CO). The pollutants may be gasses, vapours, viable or non-viable aerosols or particulate matter, allergens, etc. The risk factors also include technical causes such as ventilation, humidity and temperature. The sources of IAP are found indoors and outdoors and include humans, their activities, processes, maintenance, furniture, etc.

Perceptions of body functioning

In recent investigations symptoms related to mucous membranes in eyes, nose, mouth, and throat are symptoms frequently related to poor IAQ (Skyberg et al 2003, Peitersen et al 2006). These symptoms are reported from office buildings (Reijula et al 2004, Wolkoff et al 2006) or buildings with low ventilation (Wargochi et al 2000). Symptoms have been related to house or office dust exposures (Pan et al 2000; Skulberg et al 2004, Chao et al 2003), chemical contaminants from the sewer system and damp construction materials (Putus et al 2004), and with mould exposure (Ebbehøj et al 2005; Hirvonen et al 1999; Park et al 2006). Pharyngeal dryness increased when temperatures rose and was alleviated with a rise in relative humidity (Reinikainen et al 2003). Symptoms related to skin areas are frequently reported from field surveys (Skyberg et al 2003). Recently reported or suggested causes are exposures to mould (Ebbehøj et al 2005), storing of organic waste in the home (Herr et al 2004a,b), and house or office dust (Skulberg et al 2004). Examples of respiratory symptoms are cough, tightness of breast, asthmatic symptoms, phlegm, wheeze, chest tightness, attacks of shortness of breath, and attacks of cough. These symptoms are reported from buildings with low ventilation (Wargochi et al 2000). Chemical contaminants from sewer system and damp construction materials (Putus et al 2004) exposures to house or office dust (Pan et al 2000; Herr et al 2004b), mould exposures (Hirvonen et al 1999; Putus et al 2004; Chao et al 2003) have been suggested as cause. Significantly increased lower respiratory symptoms were associated with Endotoxin in floor dust (Park et al 2006). In field surveys, symptoms related to CNS and performance are frequent (Skyberg et al 2003). Examples are difficulty in thinking clearly, concentration difficulty, headache, feeling of fatigue, heavy-headedness, sluggishness, sleepiness, nausea, etc. These symptoms are reported from buildings with poor ventilation (Wargochi et al 2000). The symptoms are often work-related (Reijula et al 2004). Occupants in open-plan offices more frequently complain about CNS symptoms than occupants in multi-person and cellular offices (Peitersen et al 2006). Some reported or suggested causes are house or office dust (Pan et al 2000) and moulds in the indoor environment (Hirvonen et al 1999; Ebbehøj et al 2005).

Environmental perceptions

Dampness in dwellings, with emissions of odorous compounds, is associated with an increase in symptoms (Engvall et al 2002). The indoor climatic conditions seem to influence the perception of odours. Any kind of humidity seems to increase odour sensation (Reinikainen et al 1997, 2003). A combination of odours and signs of high humidity in buildings was related to an increased occurrence of all symptoms (Engvall et al 2002). Increasing ventilation decreased the percentage of subjects' odour reports, and increased the perceived freshness of air (Wargochi et al 2000). N.Trigeminus and the chemical sense for irritation are found in mucous membranes of nose and eyes, and facial skin.

Processed evaluations and syndromes

Occupants in open-plan offices are more likely to perceive poor air quality than occupants in

multi-person and cellular offices (Peitersen et al 2006, Reijula et al 2004, Wargochi et al 2000). The recently reported or suggested causes are chemical contaminants from the sewer system and damp construction materials (Putus et al 2004), with mould exposure (Ebbehøj et al 2005), lack of office cleanliness, and low job satisfaction (Chao et al 2003). Processed ratings such as perceived "Air Quality" may be significantly correlated with other responses (Pan et al 2000). Recently several groups have discussed a prioritising of the most IAQ relevant compounds (WHO 2006, 2007, Cochet et al 2006, Kotzias et al 2005, Anonymous 2006).

Epidemiology: incidence/prevalence of the disease, risk attributable to IAQ, time trend

Definition of exposure scenario and risk groups

The rights of the population to healthy indoor environments are specified in a WHO document (Mølhave et al 2000). The exposure scenario and risk groups relevant to symptoms and perceptions indoors include in principle the entire population, the exposures it receives in all build environments during a whole life. The population to consider includes the whole population, of all ages, both genders, and all sensitivities, etc. Excluded are build environments with special requirements or regulation. Examples of such excluded indoor environments are industrial work places, hospitals, transportation etc. These environments are excluded because of special pollutants, sources, or persons at especial high risk e.g. because of diseases.

Incidence/prevalence of buildings with increased discomfort and increased frequency of symptoms and the risk attributable to IAQ

The fraction of the incidence/prevalence of reports of discomfort and symptoms which can be related to indoor air quality is not exactly known. However, in buildings without specific complaints of poor IAQ the prevalence is often close to zero and normally below 30% of the occupants. In affected buildings the prevalence often ranges between 50 and 100% of the occupants. The most frequent effects related to indoor air quality (IAQ) seem to be acute physiological or sensory reactions, psychological reactions, and subacute changes in sensitivity to environmental exposures (Berglund et al 1992). Objective, adverse health effects of poor IAQ are well known but rare compared to the prevalence of unwanted symptoms and perceptions (Berglund et al 1992). Because of the unclear and subjective nature of evaluations and complaints no clear definitions exist for the unacceptable prevalence and no reference values or golden standards exist on which conclusions can be based. In the literature, the levels of prevalence, which have been called abnormal range from 10% to 100% depending on the symptom or perception in question. There is good and substantial evidence for the relation between Indoor Air Pollutants (IAP) and symptoms and perceptions (Berglund et al 1992).

Productivity and absenteeism has been related to IAQ. Results from a preliminary study yield a significant association between classroom-level ventilation rate and test results of student performances on standardized aptitude tests that are administered to students on a yearly basis (Shaughnessy et al 2006).A review of 23 studies suggests that a linkage exists between typical BRIs and productivity indicators such as task or work performance or absence from work. Quantitative associations between BRS and productivity were demonstrated in two office environments (Niemela et al 2006).The existing literature indicates that ventilation has a significant impact on several important human outcomes including task performance and productivity among occupants or sensory panels (Seppanen et Fisk 2004). The size of the decrease of productivity in most aspects of office work performance appears to be as high as 6-9%, the higher value being obtained in field validation studies (Wyon 2004).In an intervention study the performance of four simulated office tasks improved monotonically with increasing

ventilation rates, and the effect reached formal significance in the case of text-typing. For each two-fold increase in ventilation rate, performance improved on average by 1.7% (Wargocki et al 2000).Another intervention study indicated that the indoor air quality improved productivity by 11%, compared with a 4% reduction of productivity among the control group of workers (Menzies et al 1997).Recent studies show that improvement of IAQ by a factor of 2-7 compared with existing standards increases office productivity and school learning significantly, while decreasing the risk of allergic symptoms and asthma in homes (Fanger 2006).

Time trend related to indoor pollution

The incidence/prevalence of discomfort and symptoms has been changing over time reflecting changes of the exposure the population receives and of the sensitivity of the population. In addition the population may have changed its risk perception and thus register and respond to symptoms which previously would have gone unreported. Important factors are reduction of the ventilation to save energy, introduction of new building materials and construction procedures, new consumer products, and an increased fraction of the population with different types of hypersensitivities. Through the last 50 years many changes have happened up and down in such factors but because of the unspecific nature of the symptoms the overall trend of the prevalence for the entire mass of buildings has been rather stable.

Impact of indoor pollution to the burden of diseases and cost estimates

The burden (both economically and in changed wellbeing) caused by symptoms and discomfort related to indoor air pollution is unknown. The economical costs include both losses experienced by the individual, costs induced on the local network or organization which this individual is part of (e.g. renovation of buildings or sick leave) and costs inflicted onto the society e.g. in the form of medical therapy or early retirements. Added to this are indirect costs e.g. related to guideline setting and their enforcement and control.

The following is a constructed example illustrating the costs of poor IAQ in a typical office building. The building is assumed to be a suburban 14 story office building, each floor of 500 m^2, and it was built in 1980. The estimated price of the building is US$ 6 000 000. The ventilation system has a heating and cooling system for a temperate climate. The energy consumption is US$ 15/m^2 or US$ 105 000 each year. There are 30 employees on each floor, i.e. 420 employees. The average annual salary is US$ 35.000 corresponding to a total annual salary of US$ 14 700 000. Total annual turn-over of business in the building is US$ 50 000 000. A HVAC company suggest to invests US$ 200 000 in the HVAC system to optimize the system within the existing HVAC guidelines and estimate that the owner will save 50% of the energy cost corresponding to a pay-back period of 2 years. The process also includes that hazardous cooling liquids are exchanged with new environmentally acceptable liquids. This renovation is done.

One year after the expected energy savings are subsequently found (now US$ 53 000 a year) but multiple complaints about poor IAQ e.g. thermal and acoustic environment and odours are reported among the occupants. The number of lost working days due to sick leave increases from 7 to 12%. The turn-over of staff increases from 10% to 15% annually and reduced work productivity from 100% to 97% is reported but the associations to IAQ of these two last are uncertain. After four years an IAQ investigation is made by external consultants. Their recommendations are that changes should be made in the building and its HVAC system. Total price: US$ 200 000 (incl. US$ 50 000 salary). The changes result in increased operational costs to US$ 75 000. Symptoms and sick leave returns to normal. The energy savings are environmentally friendly and support the corporate goals. The trade-off is decreased well-being and work satisfaction among occupants. This is against the corporate goals and humans rights to

a healthy indoor environment. Energy savings corresponding to US$ 53 000 a year are achieved. The savings result in lost productivity due to sick leave corresponding to 5% of US$ 14 700 000 which equals US$ 735 000 a year. The annual balance is US$ 100 000 versus US$ 750 000. The more uncertain or potential loss due to decreased productivity is 3% of US$ 50 000 000 and equals US$ 1 500 000 a year. It takes 1 month to train a new employee corresponding to US$ 3 000. Therefore 21 new employees correspond to US$ 63 000.- a year.

The annual losses mentioned above continued until the renovations had been finished. In this constructed example the economical balance is US$ 3 128 000 versus US$ 288 000 in favour of including IAQ in planning of the renovation. If the more uncertain potential losses are included the balance is US$ 9 378 000 versus US$ 288 000. In both cases the future operational cost is US$75 000 a year.

Susceptible population subgroups

It is well documented that risk groups exist and many response modifying factors affect the occupants' responses. Examples of known risk factors are health status (atopy, sick persons, skin temperature), demographic data (age groups incl. children, occupation, job function, gender), life style (smoking), psycho-social loads (low social support or satisfactions, psychosocial and personal biases), exposure scenario (previous exposures, competing sensory stimulation, interactions between concurrent exposures, adaptation, accumulation, duration of exposure). Interactions between concurrent exposures and adaptation processes are characteristic of the sensory systems involved in the perception of odour and mucosal irritation, further the duration of exposure influences the perception (Berglund et al 1992).

Women report symptoms more often than men (Ebbehøj et al 2005; Reijula et al 2004; Skyberg et al 2003; Bullinger et al 1999; Runeson et al 2003, 2006). This may be an effect of less favourable working conditions under which women are employed (Bullinger et al 1999). Responding women may have a lower sense of coherence (SOC) value, a psychological measurement of a life attitude (Runeson et al 2003). Individuals who experimentally are given a harmful bias reported significantly more health symptoms following exposure indicating induction of a strong personal bias (Dalton 1999). Therefore psychosocial and personal reasons may dominate general symptoms (Ebbehøj et al 2005). Sick Building Syndrome (SBS) may be more common in younger subjects (Runeson et al 2003). Atopic disposition is a possible risk factor for skin irritation (Herr et al 2004a,b, Chao et al 2003, Runeson et al 2003, 2006, Reijula et al 2004, Skyberg et al 2003). Lifestyle including passive smoking and psychosocial load are also predictors of symptoms (Skyberg et al 2003). Also occupation, job functioning, low social support or satisfactions are risk factors (Skyberg et al 2003, Chao et al 2003, Runeson et al 2006).

Conclusions related to policy making

This review shows that not much has changed since the report of Berglund et al. (1992). The poorly defined symptoms remain poorly understood. The disability associated with IAQ symptoms and syndromes still generates controversy (Hodgson 2002).

Three types of subjective evaluations or reports related to IAQ are identified. They are "Perceived Body Functions", "Environmental Perceptions", and "Processed Reports or Evaluations". "Perceived Body Functions" describes changes in body functioning and are focussed on individual organs or tissues. "Environmental Perceptions" addresses exposure

factors in the environment. Subjective evaluations are essential for these two last types of evaluations and they can probably not be replaced by objective measurements.

No simple causal D-R relation can be expected for subjective symptoms and perceptions and unknown biases make it difficult to use occupants' reports in science and investigations as their personal biases can be strong. In real life situations, the symptoms or subjective reports prevalence's should not be used as exposure measurements and subjective reports from buildings may only qualify as screening tools. It is concluded that the use of SBS should be discouraged and replaced by multi-symptom questionnaires. Personality and personal vulnerability such as gender, age, atopy, and asthma, as well as indoor exposures, should be considered in both indoor environmental epidemiology and in practical handling of buildings with suspected indoor problem, especially when the technical investigations fail to identify any obvious technical malfunction (Runeson et al 2003, 2004, 2006). It is important to combine technical measurements or inspections with a longitudinal evaluation of occupant reactions (Engvall et al 2005) and indoor air temperature and humidity may be important for the perceived air quality and SBS symptoms (Fang et al 2004).

A WHO expert group has recommended that odours can be measured through the immediate response of the non-adapted olfactory system (visitor situations). It should be noted that odour intensity measured by visitors does not necessarily correlate with the perceptions of the occupants (WHO 1987, Berglund et al 1992). Therefore occupants' reports are also needed. Regulatory agencies now require sensitivity, validity, reliability, and biological meaningfulness of sensory methods applied for indoor air quality control (Berglund et al 1992). Therefore, investigators should use a strong quality assurance policy in IAQ evaluations based on subjective reports. However, to reduce bias a trained external panel may have to be included in IAQ investigations. Control groups and norm values in reference groups are difficult or even impossible to use in relation to IAQ. Taking this into consideration, the search for norm values or a framework seems to be of limited value (Neuner & Seidel 2006).

Objective methods may only apply for body perceptions and some environmental perceptions, and suggested indicators of activated defence mechanisms include indicators of inflammation and immune system responses, changed biomarker values in lavages, condensed exhalation, blood, and tear liquid (e.g. cytokines, cells), reddening eyes and skin, skin irritation, and rashes. Recent indications of new biomarkers for changed body functions caused by poor IAQ have appeared. Inflammatory markers may predict high prevalence of respiratory symptoms (Hirvonen et al 1999). Lu et al indicated that the urinary 8-hydroxydeoxyguanosine (8-OHdG) level was significantly associated with SBS complaints (Lu et al 2007). This is also that case for matrix metalloproteinase 9 (MMP9), leptin, and alpha melanocyte which may stimulate hormone (MSH), vascular endothelial growth factor (VEGF), immunoglobulin E (IgE), and pulmonary function (Shoemaker & House 2006). Neurological functioning may in the future be monitored objectively through visual contrast sensitivity (VCS), an indicator of neurological function, which was abnormally low in SBS patients (Shoemaker & House 2006) and performance measurements may be used as processed measurements of CNS function. Examples are errors made while typing, number of calls made in call centres, and absence from work. Physiological changes may in the future be registered objectively through blinking frequency (Nøjgaard et al 2005). Peak flow and respiratory measurements are available for respiratory effects and allergy-asthmatic changes. An interesting observation is that Shoemarker et al indicated that cholestyramine (CSM) therapy may be an effective therapy against SBS (Shoemaker & House 2006). The indicated objective methods can only be used for body perceptions, but many are themselves not real health effects but merely biomarkers which in addition also are strongly

influenced by biases.

Policy relevance of the conclusions of the studies
From the previous chapters it appears that indoor air pollutants cause unspecific effects and that these do not unambiguously identify the exposure. A multitude of biological mechanisms are involved at the same time in the responses to multiple exposures indoors and only few objective measurements are available. Some types of responses can not be replaced by objective measurements and often the effects and exposure cannot be quantified. Added to this, the resulting subjective reports are affected by bias and response modifiers. It follows that traditional toxicological procedures for the establishment of guidelines seem difficult to use for these subjective responses and evaluations and rational preventive actions therefore must take into account the level of toxicological knowledge available for different polluting agents and their health effects.From this it follows, that if IAQ guidelines are to be established based on subjective perceptions or symptoms reports three types of D-R relations must be considered and consequently also three types of guidelines. These are perceptions and symptoms with known causality, based on quantifiable effects and exposures, symptoms with unknown causality, and suggested or hypothetical causalities waiting for further investigations before rational decisions can be made.

Perceptions and symptoms with known causality: As described in the introduction, a BRI is characterized by a known causality between health and a certain exposure. At low exposure levels only unspecific symptoms may be present and often symptoms are the most sensitive effect of IAP. It follows that most IAQ guidelines for BRIs will be defined from such symptoms. At low exposure levels the presence of these unspecific symptoms does not by themselves identify the causal exposure. This exposure agents must be identified by other means e.g. measurements. Formaldehyde is an example for which a threshold for irritation/odour could be defined in the lab. Another example is asthma or COPD caused by many types of air pollutants. For these last diseases the symptomatology is important for the diagnoses. As the causality is known for perceptions and symptoms thresholds and guideline values can be defined following traditional procedures in controlled lab settings and quantifiable exposures. In this way thresholds, NOEL, and LOEL etc. can be defined or measured under conditions where interactions from other types of exposures can be excluded.

Symptoms with unknown causality: Assuming that all BRI with known traditional mono-factorial causality are dealt with as described above, it can also be assumed that all causalities which in higher exposure ranges might cause more adverse and irreversible health effects in occupants are under control. However, a group of causalities remain to be dealt with. Typically these include effects with multifactor relationships following mixtures of exposures (cocktail effects). For the reasons mentioned above, many such symptoms and perceptions in mixed real life exposures do not qualify for traditional guideline settings. A broad spectrum of causes is possibly contributing to the prevalence of individual unspecific symptoms or perceptions in any particular building and to SBS. Because of the ill-defined causality, lack of quantifiable effects and exposure measurements etc. no strict traditional guidelines can be established. However, the importance of such complaints is well documented and guidance, recommendations, labelling systems, and emission control in these cases become the preferred tool of prevention. These less strict guidelines are acceptable only for discomfort and SBS etc. and only if possible averse health effects can be excluded e.g. because all relevant exposures are under guideline regulation as mentioned above. In any case an ALARA principle should be followed. Also the combined effects of cocktail exposures are unsolved both scientifically and administratively. Some procedures based on an assumed additivity may be taken over from occupational guideline

settings. An example of the complex nature of such guidelines is Endotoxin in building dust which may indicate dampness and possible microbial growth and thus increased risk of building-related symptoms including building-related asthma, respiratory, and systemic symptoms (Park et al 2006). Building type especially open-plan offices may be a risk factor for adverse environmental perceptions and symptoms (Peitersen et al 2006).

Symptoms with hypothetical causality: Presently, no rational guidance can be given for suggested or hypothetical causalities (such as multiple chemical sensitivity (MCS)). In any case an ALARA principle should be followed.

Relevance of indoor exposure threshold levels
Several procedures for prioritizing have been suggested by which the most important pollutants of indoor air can be identified for subsequent guideline setting. However, no consensus exists. While we are waiting for missing data, substitute measures might be helpful (eg. Cochet et al 2006, Kotzias et al 2005). Several working groups have shown that principles for setting of IAQ guidelines can be defined based on combinations of existing procedures. The WHO has initiated a working group to define such guidelines and recommendations. The future guidelines may include both traditional guidelines for single compounds and a set of guidance and recommendations for healthy buildings covering situations with only minor adverse health changes or discomfort.

Many suggested objective measurements (e.g. mediators) which are in progress to be used in guideline setting are not real health effects but merely biomarkers of ongoing changes, and are strongly influenced by biases. It is often questionable if they can be used as substitute measurements. In IAQ guideline settings three types of DR relations must be considered. These are perceptions and symptoms with known causality, based on quantifiable effects and exposures (BRI), unspecific symptoms with unknown causality, and hypothetical causalities waiting for further investigations. It is concluded that future guidelines for ventilation rate based on comfort and health should no longer be independent of indoor air temperature and humidity.

For most of the health effects for which objective measurements are available D-R relations and thresholds are not available and few of the thousands of relevant chemicals have been examined at low exposure levels. Despite this some progress has been seen. Recently several groups have discussed guideline settings for the most IAQ relevant compounds (WHO 2006, 2007, Cochet et al 2006, Kotzias et al 2005, Anonymous 2006). Several procedures for prioritizing are available by which the most important pollutants can be identified. However, no consensus exists. While we are waiting for missing data, substitute measures might be helpful. At low IAQ exposure range a lowest concentrations of interest (LCI) type of estimates may be useful. Recommended low and a higher action levels may also apply (Bluyssen et al 1997). Again no consensus exists for such procedures. Under all circumstances an ALARA principle should be followed.

Because of the known causality behind a BRI, thresholds and guideline values can be defined following traditional procedures using symptoms in controlled lab settings and quantifiable exposures. In this way thresholds, NOEL, and LOEL can be defined where interactions from other types of exposures can be excluded. Some progress has been seen recently in approaching guidelines for IAQ. Several procedures for prioritizing are available by which the most important pollutants can be identified. In guideline settings apportionments between allowable contributions from different sources must be discussed. A special case of this is how indoor/outdoor fractions are coordinated in I/O guidelines.

The combined effects of cocktail exposures most be dealt with both scientifically and administratively. Some additive procedures may be taken over from occupational guideline settings. Symptoms and perceptions in such mixed real life exposures do not qualify for traditional guideline settings and guidance; instead recommendations, labelling systems, and emission control become the tool of prevention. These less strict guidelines are acceptable only for discomfort and SBS etc and only if adverse health effects can be excluded e.g. because all relevant exposures are under guideline regulation as mentioned above.

In IAQ guideline settings apportionments between allowable contributions from different sources must be discussed. We do not know how to deal with it. A special case of this is how indoor/outdoor fractions are coordinated in I/O guidelines.

Potential of building envelope and HVAC system to protect people, including the susceptible individuals

Guidelines identify exposure levels accepted for human exposures. They are, however, costly and time consuming to control through active measurements. The preferred guidelines therefore are based on source and emission control. A typical example is formaldehyde from particle boards. Such guidelines are based on an assumed ventilation of the rooms to ensure that the exposure threshold is not exceeded. Existing ventilation guidance therefore has other functions than minimizing energy consumption.

Indoor air temperature and humidity may be important for the perceived air quality and SBS symptoms (Fang et al 2004) and perceived indoor environments, non-specific symptoms, and their associations are associated with the season (Mizoue et al 2004).

It follows that a set of good practices guidance for construction, maintenance, and building usage should be developed which covers all relevant risk factors (a healthy building's regulations). The risk factors include technical causes such as ventilation, humidity and temperature, IAP sources, maintenance etc. In any case an ALARA principle should be followed.

Open questions and research needs

There is a strong need for research on:

- How humans report symptoms and perceptions.
- On biological mechanisms involved in human responses to IAQ.
- Replacement of some of symptoms and perceptions with objective measurements.
- A quality assurance policy in IAQ evaluations based on subjective reports.
- Toxicological data for IAQ relevant compounds.
- The interactions between multiple exposures (cocktail problems).

A consensus is required on:

- Procedures for prioritizing among the most important IAQ pollutants.
- Interim procedures for estimation of substitute data until more accurate toxicological data become available.
- A set of good practices for construction, maintenance and building usage should be developed for all non industrial building types which cover all IAQ relevant risk factors (a healthy building's regulations).
- Apportionments and coordination of I/O guidelines.

Table 1. Biological processes involved in response to poor IAQ

- The chemical sense for odorants and irritants in face, eyes, and nose
- Unspecific pain/irritative receptors in skin
- Vision
- Immune responses
- Inflammatory responses
- Body signalling systems
- Mediators
- Neural reflexes
- Interpretation in CNS

Table 2. Perceptions, symptoms, well-being, and other subjective health effects in relation to IAQ

- Perceptions of body functioning, symptoms of malfunction of body functioning
  - Eyes, nose, mouth, throat
  - Skin
  - Indicators of respiratory malfunction, asthma, allergic responses, non immune based responses, bronchial constriction
  - Indicators of CNS malfunction, performance, and productivity

- Environmental perceptions
  - Odours, n. Olfactorius, odour masking, adaptation.
  - Irritation n. Trigeminus

- Processed reports or evaluations
  - General well being
  - Indoor Air Quality
  - Sick Building Syndrome (SBS)
  - Productivity and learning

Table 3. The Sick Building Syndrome (Berglund et al 1992): A high proportion of the occupants of the building must be reacting, and the 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, increased absenteeism
- Contacts to 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 e.g. in the form of high exposure to single agents.

References

Anonymous, Guidance for setting occupational exposure limits: Emphasis on data-poor substances. Report no. 101. 2006. pp.1-86. ECETOX, Brussels, Belgium.

Berglund,B., Brunekreef,B., Knöppel,H., Lindvall,T., Maroni,M., Mølhave,L., Effects of Indoor Air Pollution on Human Health. Indoor Air 1992; 2:2-25.

Bullinger M., Morfeld M., von Mackensen S., Brasche S. The sick-building-syndrome--do women suffer more? Zentralbl.Hyg.Umweltmed. 1999; 202: 235-241.

Bluyssen,P.M., Cochet,C., Fischer,M., Knöppel,H., Levy,L., Lundgren,B., Maroni,M., Mølhave,L., Rothweiler,H., Saarela,K., Seifert,B., Evaluation of VOC emissions from building products, Solid flooring materials. Report 18, EUR 17334EN Ed. 1997. Pp 1-109, Eurpoean Commission, JRC, Ispra, Italy.

Chao H.J., Schwartz J., Milton D.K., Burge H.A. The work environment and workers' health in four large office buildings. Environ.Health Perspect. 2003;111: 1242-1248.

Cochet,C., Fernandes,E.O., Jantunen,M., Lindvall,T., Maroni,M., McLaughlin,J.P., Mølhave,L., Seifert,B., Strategies to determine and control the contributions of indoor air pollution to total inhalation exposure (STRATEX), EUR 22503, Report 25. 2006. pp 1-77. European Commission, Joint Research Center, Ispra, Italy.

Cometto-Muniz JE, Cain WS, Abraham MH () Detection of single and mixed VOCs by smell and by sensory irritation. Indoor Air 2004;14 Suppl 8: 108-117.

Dalton P. Cognitive influences on health symptoms from acute chemical exposure. Health Psychol. 1999; 18: 579-590.

Ebbehøj N.E., Meyer H.W., Wurtz H., Suadicani P., Valbjorn O., Sigsgaard T., Gyntelberg F. Molds in floor dust, building-related symptoms, and lung function among male and female schoolteachers. Indoor Air 2005; 15 Suppl 10: 7-16.

EU European Concerted Action "Indoor Air Quality and its Impact on Man" Sick Building Syndrome - a Practical Guide, (Report No. 4). EUR 12294 EN, 1989. Commission of the European Communities, Luxembourg,

Fang L., Wyon D.P., Clausen G., Fanger P.O. Impact of indoor air temperature and humidity in an office on perceived air quality, SBS symptoms and performance. Indoor Air 2004;14 Suppl 7: 74-81.

Fanger, O.P., What is IAQ? Indoor Air 2006. 16, 328-334.

Engvall,K., Norrby,C., Norback,D., Ocular, airway, and dermal symptoms related to building dampness and odors in dwellings. Arch Environ Health 2002; 57: 304-310.

Engvall,K., Wickman,P., Norback,D., Sick building syndrome and perceived indoor environment in relation to energy saving by reduced ventilation flow during heating season: a 1 year intervention study in dwellings. Indoor Air 2005; 15: 120-126.

Herr C.E., zur N.A., Stilianakis N.I., Gieler U., Eikmann T.F. Health effects associated with indoor storage of organic waste. Int.Arch.Occup.Environ.Health 2004a; 77: 90-96.

Herr,C.E., Nieden,A.A., Stilianakis,N.I., Eikmann,T.F., Health effects associated with exposure to residential organic dust. Am J Ind Med 2004b; 46: 381-385.

Hirvonen M.R., Ruotsalainen M., Roponen M., Hyvarinen A., Husman T., Kosma V.M., Komulainen H., Savolainen K., Nevalainen A. Nitric oxide and proinflammatory cytokines in nasal lavage fluid associated with symptoms and exposure to moldy building microbes. Am.J.Respir.Crit Care Med. 1999; 160: 1943-1946.

Kotzias,D., Koistinen,K., Kephalopoulos,S., Schlitt,C., Carrer,P., Maroni,M., Jantunen,M., Cochet,C., Kirchner,S., Lindvall,T., McLaughlin,J., Mølhave,L., Fernandes,E.O., Seifert,B., The INDEX project: Critical appraisal of the setting and implimentation of indoor exposure limits in the EU. Final report. EUR21590 Ed. Pp.1-331. 2005. European Commission, Joint Research Center, Ispra, Italy.

Hodgson M. Indoor environmental exposures and symptoms. Environ Health Perspect 2002; 110 Suppl 4: 663-667.

Lahtinen,M., Sundman-Digert,C., Reijula,K., Psychosocial work environment and indoor air problems: a questionnaire as a means of problem diagnosis. Occup Environ Med 2004. 61; 143-149.

Lu C.Y., Ma Y.C., Lin J.M., Li C.Y., Lin R.S., Sung F.C. Oxidative stress associated with indoor air pollution and sick building syndrome-related symptoms among office workers in Taiwan. Inhal.Toxicol. 2007; 19: 57-65.

Menzies,D., Pasztor,J., Nunes,F., Leduc,J., Chan,C.H., 1997. Effect of a new ventilation system on health and well-being of office workers. Arch Environ Health 52, 360-367.

Mizoue T., Andersson K., Reijula K., Fedeli C. Seasonal variation in perceived indoor environment and nonspecific symptoms in a temperate climate. J.Occup.Health 2004; 46: 303-309.

Mølhave, L. Boschi N., Krzyzanowski M., Aas K., Bakke J.V., Bencko V., Chuchkova M., Cochet C., Farkas I., Garriga-Trillo, AKakari, . S. Kalliokoski, P. Kessel, A. Levin, H. Lindvall, T. McLaughlin, J. Mocsy I., Muzi G., Pickering A., Seifert B., Slotova K., Soskolne, C.L.and Tallacchini, M. (2000) The right to healthy indoor air, Report of a WHO Meeting, WHO Regional office for Europe, Copenhagen, Denmark.

Neuner R., Seidel H.J. Adaptation of office workers to a new building - impaired well-being as part of the sick-building-syndrome. Int J Hyg Environ Health 2006; 209: 367-375.

Niemela R., Seppanen O., Korhonen P., Reijula K. Prevalence of building-related symptoms as an indicator of health and productivity. Am.J.Ind.Med. 2006; 49: 819-825.

Nøjgaard J.K., Christensen K.B., Wolkoff P. The effect on human eye blink frequency of exposure to limonene oxidation products and methacrolein. Toxicol.Lett. 2005; 156: 241-251.

Pan Z., Mølhave L., Kjaergaard S.K. Effects on eyes and nose in humans after experimental exposure to airborne office dust. Indoor Air 2000; 10: 237-245.

Park J.H., Cox-Ganser J., Rao C., Kreiss K. Fungal and endotoxin measurements in dust associated with respiratory symptoms in a water-damaged office building. Indoor Air 2006; 16: 192-203.

Pejtersen J., Allermann L., Kristensen T.S., Poulsen O.M. Indoor climate, psychosocial work environment and symptoms in open-plan offices. Indoor Air 2006; 16: 392-401.

Putus T., Tuomainen A., Rautiala S. Chemical and microbial exposures in a school building: adverse health effects in children. Arch.Environ.Health 2004; 59: 194-201.

Reijula K., Sundman-Digert C. Assessment of indoor air problems at work with a questionnaire. Occup.Environ.Med. 2004; 61: 33-38.

Reinikainen, L.M., unela-Tapola, L., Jaakkola, J.J., Humidification and perceived indoor air quality in the office environment. Occup Environ Med 1997; 54, 322-327.

Reinikainen L.M., Jaakkola J.J. Significance of humidity and temperature on skin and upper airway symptoms. Indoor Air 2003; 13: 344-352.

Runeson R., Norback D., Stattin H. Symptoms and sense of coherence--a follow-up study of personnel from workplace buildings with indoor air problems. Int. Arch. Occup. Environ. Health 2003; 76: 29-38.

Runeson R,. Norback D., Klinteberg B., Edling C. The influence of personality, measured by the Karolinska Scales of Personality (KSP), on symptoms among subjects in suspected sick buildings. Indoor Air 2004; 14: 394-404.

Runeson R., Wahlstedt K., Wieslander G., Norback D. Personal and psychosocial factors and symptoms compatible with sick building syndrome in the Swedish workforce. Indoor Air 2006; 16: 445-453.

Seppanen,O.A., Fisk,W.J., Summary of human responses to ventilation. Indoor Air 2004. 14 Suppl 7, 102-118.

Shaughnessy,R.J., Haverinen-Shaughnessy,U., Nevalainen,A., Moschandreas,D., A preliminary study on the association between ventilation rates in classrooms and student performance. Indoor Air 2006. 16, 465-468.

Shoemaker R.C., House D.E. Sick building syndrome (SBS) and exposure to water-damaged buildings: time series study, clinical trial and mechanisms. Neurotoxicol.Teratol. 2006; 28: 573-588.

Skulberg K.R., Skyberg K., Kruse K., Eduard W., Djupesland P., Levy F., Kjuus H. The effect of cleaning on dust and the health of office workers: an intervention study. Epidemiology 2004; 15: 71-78.

Skyberg K., Skulberg K.R., Eduard W., Skaret E., Levy F., Kjuus H. Symptoms prevalence among office employees and associations to building characteristics. Indoor Air 2003; 13: 246-252.

Wargocki,P., Wyon,D.P., Sundell,J., Clausen,G., Fanger,P.O. The effects of outdoor air supply rate in an office on perceived air quality, sick building syndrome (SBS) symptoms and productivity. Indoor Air 2000; 10: 222-236.

WHO, The WHO definition of Health. Proceedings and final acts of the international health organization conference in New York 19-22/7, 1946. UN/WHO Interim Commission, Newark, USA, 1948. pp. 100-130.

WHO, World Health Organization. Air Quality Guidelines for Europe, (European Series No. 23) 1987. WHO Regional Office for Europe. Copenhagen, Denmark,

WHO. Development of WHO Guidelines for indoor air quality, Report of a working group meeting, Bonn, Germany 23-24 October, 2006. EOR/05/5067585 Ed. WHO regional office for Europe, Copenhagen, Denmark. 2006.

World Health Organization (WHO) Working group on: WHO guidelines on indoor air quality: Dampness, mould and ventilation, 2007. WHO, Bonn, Germany.

Wolkoff P., Skov P., Franck C., Petersen L.N. Eye irritation and environmental factors in the office environment--hypotheses, causes and a physiological model. Scand.J.Work Environ.Health 2003; 29: 411-430.

Wyon,D.P., The effects of indoor air quality on performance and productivity. Indoor Air 2004. 14 Suppl 7, 92-101.