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Review

Influence of indoor factors in dwellings on the development of childhood asthma

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ABSTRACT

Asthma has become the most common, childhood chronic disease in the industrialized world, and it is also increasing in developing regions. There are huge differences in the prevalence of childhood asthma across countries and continents, and there is no doubt that the prevalence of asthma was strongly increasing during the past decades worldwide. Asthma, as a complex disease, has a broad spectrum of potential determinants ranging from genetics to life style and environmental factors. Environmental factors are likely to be important in explaining the regional differences and the overall increasing trend towards asthma's prevalence. Among the environmental conditions, indoor factors are of particular interest because people spend more than 80% of their time indoors globally. Increasing prices for oil, gas and other sources of primary energy will further lead to better insulation of homes, and ultimately to reduced energy costs. This will decrease air exchange rates and will lower the dilution of indoor air mass with ambient air. Indoor air quality and potential health effects will therefore be an area for future research and for gaining a better understanding of asthma epidemics. This strategic review will summarize the current knowledge of the effects of a broad spectrum of indoor factors on the development of asthma in childhood in Western countries based on epidemiological studies. In conclusion, several epidemiological studies point out, that indoor factors might cause asthma in childhood. Stronger and more consistent findings are seen when exposure to these indoor factors is assessed by surrogates for the source of the actual toxicants. Measurement-based exposure assessments for several indoor factors are less common than using surrogates of the exposure. These studies, however, mainly showed heterogeneous results. The most consistent finding for an induction of asthma in childhood is related to exposure to environmental tobacco smoke, to living in homes close to busy roads, and in damp homes where are visible moulds at home. The causing agents of the increased risk of living in damp homes remained uncertain and needs clarification. Exposure to pet-derived allergens and house dust mites are very commonly investigated and thought to be related to asthma onset. The epidemiological evidence is not sufficient to recommend avoidance measures against pet and dust mites as preventive activities against allergies. More research is also needed to clarify the potential risk for exposure to volatile and semi-volatile organic compounds due to renovation activities, phthalates and chlorine chemicals due to cleaning.

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Introduction

In most countries worldwide people spend more than 80% of their time indoors. This high, overall percentage of time spent indoors is dependent on geographical area, age, job activities, sex, season and climatic conditions. Indoor air quality and its potential health consequences are much less investigated in comparison to ambient air pollution concentration. This unbalance is presumably caused by the regulator's perspective. Ambient air quality can be better regulated by emission control than indoor air pollution concentrations. This is because these concentrations are substantially impacted by the occupant's behaviour in terms of life style factors such as smoking, ventilation activity, known or unknown acceptance of major indoor air pollutants, etc.

Another factor influencing air exchange rates is the accessibility of energy sources. The increasing prices for oil, gas and other sources of primary energy will lead to better insulation of homes to spare energy costs. The better insulation of homes could lead to higher concentrations of certain air pollutants indoors.

We confine this review to indoor air in dwellings. The goal of the review is to provide a comprehensive summary of epidemiological studies on indoor factors in dwellings in relation to the onset of

childhood asthma. This review is being both a review of reviews and selected specific studies, depending on the level of knowledge. We refer this type of review later as strategic review in order to disentangle from a systematic review.

Epidemiology of childhood asthma and asthma determinants

Asthma has become the most common disease in childhood in industrialized countries (Eder et al., 2006). The International Study on Asthma and Allergy in Childhood (ISAAC), which was conducted with more than 500,000 children aged 6–7 and 13–14 years, showed a huge geographical variation in the prevalence of asthma. This variation ranged from less than 2% to more than 20% in some countries (Asher et al., 2006; Bousquet et al., 2008, 2009). Asthma, even if it is under regular medical control, strongly impacts the daily life of children. Children with asthma have been found to have differences in their social life and school performance (Bousquet et al., 2008). The reasons for the huge worldwide geographical variations and the increasing trend of asthma in childhood have not been completely understood yet. However, there are some speculations in terms of the so-called "hygiene hypothesis," in concert with the 'western lifestyle factor pattern,' which seems to be the best explanation we currently have in our hands. Indoor factors such as well insulated and less crowded homes are examples which are associated with a "western lifestyle".

Definition of asthma and prevalence in childhood

Asthma is a complex chronic inflammatory disease of the airways with reversible airway obstruction as a key characteristic (Eder et al., 2006). Clinicians diagnose asthma on the bases of one's medical history; a physical examination, including a lung function test; a longitudinal assessment of reversibility of airway obstruction; and the exclusion of other diseases with similar symptoms. However, this diagnosis strategy cannot be used in an epidemiological study because the reversibility of airway obstruction can only be tested by repeated medical examination, and this is not possible when dealing with large population samples. Thus far, there is no commonly accepted set of criteria to identify asthma in epidemiological studies. For this review we have to follow the definition which was commonly used in observational studies regardless of their justified critics. Therefore, this review will use:

(i) Asthma onset on the bases of incidence and prevalence studies using 'doctor's diagnosed asthma'
(ii) Wheezing with and without asthma medication

Each of these asthma categories has pros and cons in epidemiological settings.

Epidemiological approach to identify risk factors for asthma

The identification of risk factors for a complex disease such as asthma is a challenge that needs to be kept in mind in any review of the evidence for the role of indoor air factors. If risk factors for developing asthma are studied, one must assume that some children born without asthma will develop it as a result of exogenous or endogenous factors. If a child becomes asthmatic, he/she may suffer from acute episodes of obstruction that lead to respiratory symptoms requiring acute medication or further medical help. Thus, we have to distinguish between factors that trigger acute episodes of airway obstruction in asthmatics from those that cause the development of asthma (Eder et al., 2006). Factors that trigger acute episodes such as ambient air pollutants are best investigated with a panel study design. This type of study will not be reviewed here. For this review we will focus on risk factors involved in the incidence and prevalence of asthma; in other words, we will consider risk factors that have a high potential to cause asthma.

We will categorize the approaches for the exposure assessment. We will always start with the potential source of the indoor pollutant with a rather complex (and presumably low valid) exposure assessment approach, which is referred later to 'proxy variable'. These proxy variables will be combined with more specific scenarios of the exposure assessment which include indoor measurements.

The concept of causality in epidemiology

The issue of causality when indoor air indicators are reviewed is of central importance. In general, epidemiological research is investigating associations but not causes. A set of criteria by which the overall quality of the evidence of the association between risk factors and diseases could be made was suggested several decades before (Hill, 1965). Here we will use a set of criteria for the assessment of study quality and validity, which is used by U. S. Department of Health and Human Services 2004 in combination with criteria proposed by Bates (1992). This synthesis is a combination of the theoretical concept of causality, statistical analyses, inference, judgement, and coherence criteria. This set of criteria was applied to the topic of this review (Table 1).

Aim of this review

This strategic review aims to summarize and to evaluate the results of epidemiological studies on a broad spectrum of indoor factors and asthma onset in childhood.

Methods of this review

This is a strategic review which summarizes published papers in English in peer-reviewed journals with a specific focus of the last decade and "westernized" countries. We did not include indoor factors in dwellings of developing countries, because some of these indoor factors such as burning of biomass fuel in open fire places indoors are very specific and are not common in 'westernized' countries. Whenever a systematic review is published on a specific indoor factor or indoor air pollutant this systematic review will be referenced in detail. No extensive evaluation of a specific study can be provided in this review if numerous studies on the same topic were published. However, for some indoor factors only very little data have been published so far. For those studies, an evaluation for a single study will be made.

Results and discussion: indoor air chemicals and childhood asthma

Environmental tobacco smoke (PM and a variety of several toxic chemical substances)

Assessment of environmental exposure to tobacco smoke

Environmental tobacco smoke (ETS) exposure is here synonymously used as passive smoking or exposure to second hand smoke. It is defined as the breathing in of tobacco combustion products of smoking by non-smoking persons (Jaakkola and Jaakkola, 1997). ETS is the most important indoor pollutant and has far reaching public health relevance. Tobacco smoke contains more than 4000 chemical substances which have known or suspected carcinogenic, mutagenic, toxic or inflammatory properties (California EPA, 1997). Due to this broad range of adverse health effects, a variety of health

Table 1
Criteria for strength of causal influence based on valuable data.

A. Sufficient evidence to infer a causal relation between indoor air concentration and childhood asthma
Evidence is sufficient to conclude that there is a causal association. That is, an association has been observed between an indoor air factor and asthma in childhood where bias and confounding variables can be ruled out with reasonable confidence. If several small studies that are free from bias and confounding show an association that is consistent on magnitude and direction, this may constitute sufficient evidence for an association.
B. Suggestive but not sufficient evidence to infer a causal relation
Evidence is suggestive of an association between a surrogate of a certain indoor air factor and asthma incidence. The relationship between the indoor air concentration itself and asthma, though limited because of chance, bias and confounding, could not be ruled out with confidence. For example, if at least one high quality study shows a positive association but the results of other studies of good quality are inconsistent, this may constitute limited evidence of an association.
C. Inadequate/insufficient evidence to infer the presence or absence of a causal relation.
The available studies of insufficient quality, consistency or statistical significance are what permit a conclusion regarding the presence or absence of an association. For example, if studies fail to control a confounding variable or have inadequate sample size this may constitute inadequate or insufficient evidence to determine whether an association exists.
D. Evidence is suggestive of no causal relation
There are several adequate studies covering the full range of exposure levels that humans are known to encounter. They are mutually consistent in not showing a positive association between exposure to indoor air concentration, or a surrogate of it, and asthma onset on any level of exposure. A conclusion of 'no association' is in evitable limited to the conditions, level of exposure and length of observation covered by the available studies. In addition, the possibility of a very small elevation in risk at the levels of exposure studies can never be excluded.

outcomes, such as cancer, cardiovascular diseases, pregnancy disorders, birth outcomes and respiratory health concerns have to be considered as consequences of exposure to ETS (California EPA, 1997). For infants and children, exposure to ETS due to maternal smoking during pregnancy is of particular importance.

Exposure to ETS can be assessed by measuring nicotine in indoor air, particulate matter concentrations indoors, indoor carbon monoxid or bio-monitoring. This latter assessment is done by measuring nicotine or cotinin – a major metabolite of nicotine – in urine, blood or other biosamples as biomarkers. However, exposure to ETS is most commonly measured by questionnaires. Each of this type of assessment has specific pros and cons (Pirkle et al., 1996; Heinrich et al., 2005). The assessment of exposure to ETS by questionnaires has the advantage of being a rather cheap approach that covers a longer period of time and can also be assessed retrospectively. With a shelf-life of 12–24 h, nicotine and cotinine concentrations in urine or in the blood allow only the assessment for the exposure to ETS during a few hours or a few days after sampling of the blood or the urine.

The assessment by questionnaire is by far the most common approach to study health effects of the exposure to ETS.

Prevalence of exposure to ETS in children

The Global Youth Tobacco Survey (GYTS, 2007) covers children aged 13–15 years and asks whether they were living in homes where others smoke in their presence. This survey is focused on those countries with previously unknown proportions of children who are exposed to ETS. This survey comprises countries in Central and Eastern Europe, Central Asia, the Kaukasus area and the Balkans. The proportion of children of 13–15 years of age that are exposed to ETS in their homes ranged from 40 to 97%. This is much higher than the proportion of children exposed to ETS in Western Europe, which ranges from 20 to 58% (WHO, 2003; Pattenden et al., 2006).

Exposure to ETS and onset of asthma in children

More than 1000 papers published in peer-reviewed journals are related to ETS and asthma in children, and almost 100 review articles on the topic have been published so far. Out of this huge body of literature, a systematic quantitative review on parental smoking and prevalence of asthma and respiratory symptoms in children was published ten years earlier (Cook and Strachan, 1997). The pooled odds ratios for parental smoking were 1.21 (95% CI 1.10–1.34) for asthma, 1.24 (95% CI 1.17–1.31) for wheezing, 1.40 (95% CI 1.27–1.53) for coughing. Adjustment for several confounding factors had little effect. There was also a gradient with stronger effects when the numbers of parents who smoked increased. In general, maternal smoking had a greater effect than paternal smoking. The authors of this review concluded that the relationship between parental smoking and respiratory symptoms is most likely causal. This is based on considering the magnitude of the effect estimate, the statistical significance level, the robustness to adjustment for confounding factors, the consistency of the findings in different countries and the evidence of those responses. These combined effect estimates are similar to another comprehensive review by the California EPA (EPA California, 1997). Both reviews found the strongest effect of exposure to ETS in the youngest children.

Summarizing the epidemiological finding of studies on exposure to ETS and the onset of asthma, there is sufficient evidence (category A, see Table 1) for a causal relationship between the exposures to ETS in relation to the onset and induction of asthma in childhood.

Cleaning activities

The intention of cleaning activities is to remove indoor dust, avoid the growth of indoor microbes, bleach white textile materials (laundry), or make surfaces shinier. Removal of settled house dust reduces resuspension of dust while normal activities of the dwelling occupants. However, cleaning activities are also related to two types of indoor factors which are discussed in relation to potential health effects. The most important area is related to the emissions of the usage of the cleaning agents. The other part is related to potential health hazards by re-suspension of settled dust indoors.

Strong evidence for a positive association between cleaning activities and the onset of asthma comes from several occupational exposure studies. A review of comprehensive studies on asthma in cleaning workers showed that cleaners were at an increased risk of developing asthma at an average odds ratio of approximately two to one (Nielsen et al., 2007). However, we should not to be so naïve as to transfer these findings from occupational settings to our daily cleaning activity in our homes. There are many exposure-related differences between those who are professional cleaners and those who are doing house cleaning: time, specific agents used for cleaning purposes, differences in dilution of cleaning agents, etc. However, a large, Europe-wide multicenter study in adults showed the adverse effects on the onset on asthma in adults when household cleaning agents are used often (Zock et al., 2007). A more sophisticated analysis of a follow up of the large European multicenter study (European Respiratory Health Survey) specifically investigated health effects of the domestic use of hypochloride bleach (Zock et al., 2009). Frequent bleach use was positively associated with more frequent, reported lower respiratory symptoms and a non-significant increase of bronchial hyperreactivity, but not with asthma (Zock et al., 2009).

Health effects on asthma in children

Only very few epidemiological studies have studied the association between household cleaning agent use in relation to respiratory health and asthma in children. Within a cohort of almost 14,000 children, the total chemical burden of the mothers during pregnancy and after birth were assessed by questionnaire, including disinfectants, bleach, air fresheners, window cleaners, carpet cleaners, paint and varnish, pesticides, insect killers, paint stripper and dry cleaning fluid (Sherriff et al., 2005). The combined score of the chemical burden of these components was related to a persistent, statistically increased risk for continual wheezing (OR 2.3) and non-significant increase of onset of wheeze (OR 2.0) during the first three years of life. A cross-sectional study on school aged children (10–13 years) in relation to the domestic use of bleach and atopic sensitization was performed in Belgium (Nickmilder et al., 2007). Children living in homes that were cleaned at least weekly with bleach had less atopic sensitization to indoor allergens. This finding in a children study was similar to the reported negative association between frequent bleach and atopic sensitization in adults (Zock et al., 2009). However, the children study also reported lower rates of asthma and eczema in children whose home was frequently cleaned with bleach. The authors speculated that a potential inactivation of indoor allergens by the bleaching agents could have reduced the allergen exposure. However, the attempt to test this hypothesis failed (Zock et al., 2009). A prospective birth cohort study with the retrospective assessment of the use of room disinfectants and cleaning agents was very recently reported by Krauss-Etschmann et al. (2009). They found that asthma was not associated with the current use of room disinfectants after cautious adjustment for several potential confounders. However statistically significant associations were reported for an increased risk of the development of atopic dermatitis and itchy rashes. The authors concluded that these positive associations are presumably the result of reverse causation because mothers of children with skin symptoms might be prone to more stringent cleaning procedures to avoid exposure to house dust mite or skin superinfections.

Summary on potential effects of cleaning agents and asthma

Studies in children are scarce, and their results do not allow the drawing of any final conclusion because of their high inconsistencies (category C, see Table 1).

Cleaning and re-suspension of dust and respiratory health

Cleaning activities generally lead to a re-suspension of indoor dust (Ferro et al., 2004a,b; Long et al., 2000). There are few epidemiological studies which considered cleaning activities in relation to a re-suspension of settled dust as a potential hazard for respiratory health. A cross-sectional study of almost 996 Australian children (aged 4–12 years) studied the cleanliness at home in relation to respiratory health (Cain et al., 2005). Household cleanliness was assessed by questions on how often floors were vacuumed, moped or swept; how often mattresses were vacuumed; how often bed linen was washed in hot water; how often furnishings were dry cleaned; and how often curtains were washed or dry cleaned. Also, the states of mattresses or pillow covers were considered indicators of cleanliness. Increasing cleanliness was associated with an increased risk for current wheezing but not current asthma.

A few studies used the total amount of dust sampled on living room floors or on mattress and analysed the association with respiratory health (Gehring et al., 2007). Higher amounts of mattress were associated with a significantly decreased risk of allergic sensitization to inhalant allergens. Asthma was not considered in this study.

In summary regarding cleanliness at home and asthma, there is no indication that increased cleanliness might protect against the onset of asthma in children. In light of several studies which looked at endotoxin as a marker for bacterial growth indoors and dirtiness expressed as EU per surface, it was postulated that dirt indoors might even have preventive properties in relation to the onset of asthma.

Emissions from gas cooking (NO_2, HONO, UFP)

Gas use for cooking

Gas cooking is very common across Europe. A large population based study in young adults showed that gas cooking ranged from 6.5% in Goteborg, Sweden, to 95.5% in Grohningen, NL. Beyond the Swedish population, subjects of other western European countries such as Germany, the Netherlands, Ireland, UK, Belgium, France, and Spain used gas fuel for cooking even more than 50% (Jarvis et al., 1998). Overall, less than approximately 50% of those homes which use gas fuel for cooking purposes also use a fan. This ranges from less than 20% in Germany and more than 80% in the Netherlands (Jarvis et al., 1998). Cooking with gas is by far the most important source of indoor NO_2 concentrations in Europe. With the exception of the unflued gas heaters, which are used in Australia, heating with gas in Europe has only a small contribution to indoor NO_2 concentrations that is much smaller than gas cooking. A large European-wide study INDEX found very high NO_2 levels in homes due to the use of gas appliances (such as gas cooking or heating) ranging from 180 to 2500 $\mu g/m^3$ (Kotzias et al., 2005). In non-gas using homes of this study NO_2 indoor concentrations ranged between 13 and 62 $\mu g/m^3$ (Kotzias et al., 2005). Compared to other continents, indoor NO_2 concentrations in Europe are more or less the same as in North America (Levy et al., 1998) but are lower than in Asia (Levy et al., 1998; Shima and Adachi, 2000; Leung et al., 1998) and in particular Australia where kerosin heaters are a major source of indoor NO_2 concentrations (Nitschke et al., 1999).

Other sources of indoor NO_2

Besides cooking or heating with gas, there are several other minor sources: ambient NO_2 from vehicle exhaust might penetrate indoors and lead to increased NO_2 levels (Cyrys et al., 2000), smoking and burning candles might lead to slightly increased levels of indoor NO_2 concentrations.

In the absence of these indoor NO_2 sources, indoor concentrations will be lower than outdoor levels (0.5–0.9). Thus, indoor–outdoor ratios have been found to be below 1 (Cyrys et al., 2000). In addition to these minor indoor sources, ventilation and the volume of a room has an impact on the indoor concentrations when an indoor NO_2 source is present.

Experimental studies

Numerous experimental studies have investigated the effects of NO_2 in in vitro studies, animal experiments and human exposure studies. The findings of these studies can be summarized according to a WHO report (2005) as follows.

In vitro studies and animal experiments found the destruction of alveola and air space enlargement, changes in feature characteristics for humans such as COPD (increased mucus production and progressive airway obstruction), an atopic inflammatory response and airway hyper-reactivity in relation to high nitrogen dioxide exposure.

The results are interpreted that in vitro studies and animal studies showed which toxic effects of nitrogen dioxide might occur in humans. In light of several limitations such as high level exposure and no long-term exposure in experimental designs, these experimental studies cannot strongly support a causative relationship with adverse health effects on humans. This is in particular the case for the onset of asthma, when the relatively low levels of environmental exposures to NO_2 are considered.

Indoor NO_2 and asthma

A large number of studies have investigated the association between ambient NO_2 and the onset and exacerbation of asthma. The question is why we cannot use the findings of these studies to evaluate the association between indoor NO_2 and the onset and exacerbation of asthma. Ambient NO_2 studies with "traffic" as proxy variable might have a limited value to evaluate adverse health effects of indoor NO_2 with the proxy variable "gas cooking". Depending on different sources of NO_2 the health effects might be caused by co-pollutants, such as polycyclic aromatic hydrocarbons (PAH) or particulate matter. Thus, epidemiological indoor studies are needed to evaluate the potential health effects of indoor NO_2 exposure on asthma. The difficulty with these needed studies is related to the time consuming indoor measurements of NO_2, which need to be repeated several times because of the seasonality of the NO_2 concentrations. Therefore, several epidemiological studies were using gas cooking or use of gas appliances as a surrogate for increased indoor NO_2 concentrations. The following chapter will summarize the findings of epidemiological studies on the health effects of exposure to gas appliances and be followed by a discussion of the epidemiological evidence for an association between indoor NO_2 concentration and respiratory health – in particular the onset of asthma in childhood.

Use of gas appliances as a surrogate for indoor NO_2 exposure

The question of whether the use of gas appliances at home is associated with an increased risk for respiratory symptoms has been studied for more than 30 years. A meta-analysis of the studies conducted during the 1970s reported a combined odds ratio of 1.15 (1.09–1.22) for the association between cooking with gas and respiratory illness (Hasselblad et al., 1981).

A big study in school-aged children in Canada (n = 10,819) found that gas stove use for cooking in the home of the children was associated with current asthma (OR 1.95, 95% CI 1.40–2.68) (Dekker et al., 1991). The increased risk was cautiously adjusted for several household characteristics, like dampness and tobacco smoke at home, and also for parental educational levels as potential confounders of gas use. Analyses of data of the Third National Health and Nutrition Examination Survey found an increased risk for doctor-diagnosed asthma in children of 1.8, (95% CI 1.02–3.20) when exposed to the use of gas for cooking or heating (Lanphear et al., 2001). Also, a study in Australia found increased risk for asthma, wheezing and frequent colds when gas appliances were used at the home of young children (Volkmer et al., 1995). A birth cohort in the U.S. in high risk newborns, defined as having a sibling with asthma, found that the use of a gas stove use was associated with an increased risk of persistent coughing (1.52, 95% 1.06–2.18) in infants of mothers who did not have asthma. Within the Tasmanian infant health survey, the small proportion of children living in homes with a gas heater had an increased risk of asthma during the first seven years of life of 1.92 (95% CI 1.33–2.76) after adjustment for environmental tobacco smoke and maternal educational level (Ponsonby et al., 2000). The paper by Ponsonby et al., also reported a cross-sectional study of more than 6000 children, who showed an increased risk for wheezing (OR 1.41, 95% CI 1.17–1.71) and asthma (OR 1.33, 95% CI 1.12–1.57) when exposed to the use of gas heaters. Kerosene heaters are also very common in Australia, and they are the major source of indoor nitrogen dioxide concentrations there (Nitschke et al., 1999).

It is worthwhile to mention that all of these studies were conducted in the U.S., Canada, the U.K. or Australia. The reason is probably that gas use is rather common in these countries, and the potential health effects are of strong public health concern.

The last systematic review of respiratory health effects of cooking with gas was published almost 10 years ago (Nitschke et al., 1999). Only 3 population-based studies in children could be included in this meta analysis. Gas cooking was associated with an unadjusted risk for asthma of 1.20 (95% CI 1.11–1.30) and of wheezing (1.12, 95% CI 1.04–1.20).

Results of studies on adults (Jarvis et al., 1996, 2005) did not improve the clarity and consistency of potential associations between use of gas appliances and asthma.

Measured indoor NO_2 and respiratory health in children

Population based studies on asthma onset in children. Table 2 summarizes the study characteristics of 11 population-based studies in children with measured indoor NO_2 and respiratory health outcomes. This table also includes a few studies in infants. The 11 population-based studies are heterogeneous in terms of study type, sample size, the duration and location of indoor NO_2 measurements and analysed health outcomes. Thus, the study results are very difficult to compare and to summarize. Most of the studies except one (Shima and Adachi, 2000) used a cross-sectional study design. This only longitudinal cohort study did not found an association between indoor NO_2 and incidence asthma and wheeze. Exposure to NO_2 was mainly assessed by indoor NO_2 measurements in the bedroom, kitchen or three locations for one or two weeks. However, one study also used personal monitoring during a 24 h period (Koo et al., 1990). Out of these 11 asthma outcome studies, two found a positive association with indoor NO_2 while 8 studies did not find any association with measured indoor NO_2 levels. One study found a positive association between measured indoor NO_2 and asthma prevalence only in girls but the follow up did not show any association with incidence of asthma or wheezing over a period of three years (Shima and Adachi, 2000). Overall, the results from observational, population-based studies are so inconsistent that no final conclusion on a causal effect of indoor NO_2 on the development or onset of asthma could be drawn. There is insufficient evidence to deduce the presence or absence of a causal relation.

Nevertheless, there is a major caveat that needs to be mentioned regarding the epidemiological studies that used measured indoor NO_2 levels to assess the exposure. One might consider that the measurement based exposure is a more valid and objective assessment of exposure. However, these approaches to quantifying exposure have severe limitations, which were discussed previously (Brunekreef et al., 1990). Indoor NO_2 measurement campaigns, including the personal sampling, are restricted to a sampling period of one to two weeks, which were then repeated after a year in a few studies. All of these indoor measurements have the disadvantage of missing repeated peaks of nitrogen dioxide concentrations indoors. This is an extremely important point because it is known that strong peaks of NO_2 concentrations can occur indoors under specific conditions, like cooking with gas while the window is closed. Thus, one should be cautious to consider the integrated measurement of indoor NO_2 from one or two weeks as the better exposure estimate over asking about the use of gas for cooking purposes, frequency of cooking, ventilation while cooking, etc.

Summary on the association between emissions from gas cooking (NO_2) and asthma

Population-based studies in children found inconsistent results on the association between asthma and emissions from gas cooking or heating, assessed by the presence of gas appliances or indoor nitrogen dioxide measurements. In addition, other respiratory outcomes such as lower respiratory tract symptoms, general respiratory illnesses or even more objective markers of lung function, did not show a more consistent picture.

Some authors suggest a potential effect modification by gender and by atopy, but the gender specific results in all of the published studies are also inconsistent. In the future, a potential effect modification by genetic variants of detoxifying enzymes might be the topic of research.

Table 2
Selected studies in children that have examined associations of asthma with indoor measures of nitrogen dioxide in population-based epidemiological studies.

Study	Study type	*N*	Age	NO_2 exposures in the study	Results
Hoek et al. (1984), NL	Case–control		6 years	One week average Kitchen: 110–789 μg/m^3 Living room: 17–277 μg/m^3 Bedroom: 10–146 μg/m^3	No association of levels in any of the three locations with symptoms
Dijkstra et al. (1990), NL	Cross-sectional		6–12 years	NO_2 measurement at home	No association between elevated NO_2 and asthma and wheeze No association with lung growth
Koo et al. (1990), Hongkong	Cross-sectional	362	7–13 years	24 hour mean personal Children: 35.9 μg/m^3 Mothers: 36.5 μg/m^3	No association with asthma
Neas et al. (1991), U.S.	Cross-sectional	1500	7–11 years	Household annual average Without an NO_2 source 16.1 μg/m^3 With an NO_2 source 44.2 μg/m^3	Cumulative incidence of respiratory illness. Adjusted OR 1.4 (1.14–1.72) per 28.2 μg/m^3
Infante-Rivard (1993), CND	Case–control	457 asthmatics 457 controls	3–4 years	Twenty four hour personal average Without an NO_2 source 17.3 μg/m^3 With an NO_2 source 32.3 μg/m^3	Adjusted odds ratio for asthma was statistically significant increased
Samet et al. (1993), U.S.	Cohort	1205	Infants	Two week average bedroom 22% of measures greater than 37.6 μg/m^3	No association
Garrett et al. (1998), AUS	Cross-sectional	148	7–14 years	Bedroom Median 11.6 μg/m^3 (5.01 to 27.9 As 10th & 90th centile)	Adjusted odds ratio per 10 μg/m^3 Wheeze 1.15 (0.85–1.54) Asthma attacks 1.06 (0.77–1.46)
Shima et al., 2000, Japan	Longitudinal cohort	842	9–10 years	Mean annual living room Vented appliances 34.5 μg/m^3 Unvented appliances 60.9 μg/m^3 572ppb	Adjusted odds ratio per 18.8 μg/m^3 increase Boys Wheeze 0.98 (0.68–1.39) Asthma 0.77 (0.48–1.20) Girls Wheeze 1.90 (1.30–2.83) Asthma 1.63 (1.06–2.54) No association with incidence of wheeze or asthma over 3 year period
van Strien et al. (2004a,b)	Cohort	768	Infants born into families with asthmatic child under age of 11	Two week mean living area Interquartile range 9.6–32.7 μg/m^3	Adjusted relative rate of symptoms (1st,2nd,3rd,4th quartile of NO_2) Wheeze: 1.00, 1.15, 1.03, 1.45
Sunyer et al. (2004), Spain	Cohort	1611	Infants	Median in each of three centres 10.7 μg/m^3 22.2 μg/m^3 86.2 μg/m^3	Adjusted OR for lower respiratory tract illness <9.4 1.00 9.4 < 18.8 0.88 (0.63–1.23) 18.8 < 56.4 0.99 (0.69–1.43) 56.4+ 1.31 (0.75–2.26)
Diette et al. (2007), U.S.	Case–control	150 asthmatics 150 control	2–6 years	3 day measurements in bedroom	No association with asthma

According to the four criteria for strength of causal influence, we would categorize the association between gas use, measured indoor NO_2 concentrations and asthma in childhood to category C: inadequate/insufficient evidence to infer the presence or absence of a causal relation.

Other pollutants related to emissions from gas such as ultrafine particles and nitrous acid

Nitrous acid (HONO) is generated by a combustion process, specifically by unvented gas appliances (cooking with gas, unvented gas boilers, unvented gas heaters). It could also be produced by the absorption of NO_2 from condensed water indoors (Spicer et al., 1993). Nitrous acid is a highly reactive gas with inflammation-inducing properties. Due to its reaction with water, it was suggested that some of the heterogeneous, adverse health effects of using gas appliances might be related to a lack of measurements of HONO (Brunekreef, 2001). HONO was only measured in the framework of two epidemiological studies. In a birth cohort study of newborns having older siblings with asthma, HONO and NO_2 were measured in the living room floor. The authors found that exposure to NO_2 was more important for adverse health effects, assessed as low lung function, than exposure to HONO (van Strien et al., 2004a,b). A small study with HONO and NO_2 measurements in the kitchen of adults found an independent effect for HONO on poor lung function (Jarvis et al., 2005). Thus, a final evaluation of the role of emission of gas-derived nitrous acid can currently not be drawn.

There have been a few studies that looked at short term effects of cooking activities as a surrogate for the exposure to ultrafine particles on respiratory health symptoms. However, no single study has examined the long-term effects of these generated ultrafine particles in relation to the development of asthma. The recent expert elicitation on health effects of ultrafine particles stated a high likelihood for associations with aggravation of asthma for short-term exposure to ultrafine particles exposure only (Knol et al., 2009).

Emissions from renovation and redecoration (VOC's)

Analogous to ETS, which is related to the exposure to numerous chemicals, painting, redecoration activities, flooring and renovations, are potential increased emissions of many volatile and semi-volatile organic compounds (VOC). Dales and Raizenne (2004) pointed out that there is no universal definition of VOC and provided several supporting references. The WHO defines a volatile organic compound as one with a melting point below room temperature and a boiling point between 50 and 100 °C. These compounds

are partly, highly correlated because of their common origin. Therefore it could be extremely difficult to disentangle a potential adverse health effect between several highly correlated volatile or semi-volatile organic compounds. Thus, epidemiological studies commonly use human activities such as painting, flooring and further redecoration activities as surrogates of exposure to VOCs. The justification for this surrogate exposure scenario is based on the fact that numerous chemical concentrations are increased when homes are newly renovated (Guo et al., 2009). Some of these volatile chemicals could be shortly increased by a factor of 5 to 10 compared to the baseline level of these chemicals, which might be related to outdoor air that is penetrating indoors. Further potential sources of volatile organic compounds are tobacco smoking; emissions from building materials; and the use of consumer products like cleaning agents, cosmetics, etc. This surrogate exposure scenario has both pros and cons. One strength of this scenario is related to the fact that exposure to increased levels of a certain set of chemicals will last at least a couple of weeks, months, or even a year. This is a clear strength compared to one single measurement of volatile organic compounds because of their low repeatability even after a period of six months (Topp et al., 2004). Most of the larger epidemiological studies used a single measurement of the concentrations of VOC's to assess long-term health effects. This leads to a major misclassification in the exposure when VOC exposure is assessed by a single measurement. Another strength for the surrogate exposure scenario is that this assessment is cheap and could be done in large studies. The major disadvantage is that we do not know the specific agent which might be responsible for the observed adverse health effects and the potential of bias by unmeasured risk factor(s). Furthermore, sources other than painting activities could not be evaluated with this approach. The latter is particularly true for volatile organic compounds emitted from building material or produced by microbes (microbial volatile organic compounds-MVOC).

Painting and redecoration activities and asthma

Indirect evidence of the potentially adverse effects of indoor VOC exposure and asthma comes from a few epidemiological studies which analysed the association between redecoration and renovation and asthma. A comprehensive summary of epidemiological studies on indoor chemical source meaterials or activities and childhood asthma published until the year 2006 was published by Mendell (2007). Only one paper (Dong et al., 2008) was published beyond the review period of Mendell's reviews.

Out of the six studies in children, all of which analysed associations between renovation or painting with asthma, five studies reported positive associations for asthma or asthmatic symptoms (Diez et al., 2000, 2003; Emenius et al., 2004a,b; Jaakkola et al., 2004; Dong et al., 2008) but not one (Trevillian et al., 2005).

The few epidemiological studies may be more or less a subject of unmeasured confounding by other causal agents such as aeroallergens and mycotoxins, low ventilation conditions and dampness, and effect estimates uncontrolled for ETS. Also a potential publication bias cannot be ruled out. Thus, the data quantity and quality is too scarce to come to a final conclusion on the causal role of emissions by renovation or redecoration activities and the onset of asthma in childhood.

Volatile organic compounds and asthma

Epidemiological studies on measured VOCs and asthma or related respiratory outcomes are scarce. Most of the studies have a cross-sectional design and use one single measurement of VOC for exposure assessment. Since a single measurement is a poor indicator for a long-term exposure (Topp et al., 2004) the validity of the results is questionable. A few epidemiological studies linking measured indoor VOCs with asthma or asthma-related health outcomes will be described as follows.

An Australian case control study included 88 asthmatic cases (aged 6 months to 3 years), who attended an emergency department of a hospital, compared with 104 children of the same age without any asthma diagnosis in relation to previous painting activities in their home (Rumchev et al., 2004a,b). An indoor inventory showed that recent paintings in the homes were statistically, significantly higher in the case group compared to the controls.

Within a small German birth cohort of low birth weight babies or those with elevated total IgE in cord blood (Diez et al., 2000), the concentration of 25 VOCs were measured at home and respiratory health was monitored for one year. Increased postnatal respiratory infections, but not wheezing, were reported with increased benzene and styrene concentrations (Diez et al., 2000). Asthma was not studied because of the young age. The same group did a similar study in a population-based cohort and reported increased risk for obstructive bronchitis with increased VOCs concentrations (Diez et al., 2003) and a TH_2 shift with increased indoor exposure to VOCs (Lehmann et al., 2001).

A cross-sectional school-based study in 627 students (13–14 years of age) in Sweden reported statistically significant associations between asthma prevalence and VOCs at school (Smedje et al., 1997).

The last review on residential exposure to volatile organic compounds and asthma was published six years ago by Dales and Raizenne (2004). This review included VOC and formaldehyde and their sources: renovation activities, PVC containing wall and floor coverings. Compared to this review Dales and Raizenne (2004) used a broader spectrum of health outcomes. Dales and Raizenne (2004) concluded that observational studies have demonstrated associations between VOC and indicators of asthma. The PVC containing wall and floor coverings were associated with a clinical diagnosis of asthma. Objective measured bronchial reactivity was related to measured limonene and also to the report of freshly painted homes. In contrast to the observational studies, the intervention studies have generally failed to show a significant association. Thus, Dales and Raizenne (2004) concluded that VOC can not induce asthma in residential settings with their low level of exposure. The discrepancy between observation and intervention studies might be explained by the small size of the intervention studies, their short duration of exposure and that observational studies are potentially confounded by unmeasured risk factors for asthma (Dales and Raizenne, 2004). In the light of these criticims, and in addition the extreme high levels of exposure, the low repeatability of measured VOC in the observational studies and the published studies beyond the review by Dales and Raizenne (2004) we conclude that there is a lack of knowledge to draw a strong conclusion on the causal link between VOC exposure and asthma onset.

In summary, although indirect evidence from renovation and redecoration activities and direct evidence by measured VOCs point to a positive association with asthma, the level of evidence for positive association between these exposures and development of asthma in childhood is insufficient (category C, see Table 1).

Exposure to traffic-related pollutants penetrating indoors (near roadway studies, PM, NO_2, diesel soot, organic components)

If the major location of the exposure is indoors, then one might consider those air pollutants as an indoor air pollutant even if their origins were outside. This is especially the case for the exposure to air pollutants during infancy. Infants are breathing indoor air at home most of the time. Therefore, we considered birth cohort studies which recruited cohort members before or at birth as relevant for exposures in dwellings although the air pollutants may have had their origins out of doors. Further reasons for restricting the review on birth cohorts are that a comprehensive review was recently published (HEI, 2010), which included results from all

types of epidemiological studies together with toxicological experiments. Therefore, studies in school environments were also not considered in this review.

Table 3 summarizes the 7 birth cohorts which used individualized exposure assessments to traffic-related pollutants at residential addresses starting at birth.

In the following the main findings of the 7 studies will be described. The Dutch PIAMA cohort (Brauer et al., 2002, 2007) and the Munich GINI/LISA cohort (Gehring et al., 2002a,b; Morgenstern et al., 2007, 2008) used a similar land use regression model to assess the exposure to traffic-related pollutants at residential addresses at birth and during the first 6 years of life (Brauer et al., 2003). The Swedish birth cohort BAMSE (Nordling et al., 2008; Melén et al., 2008) and the Oslo birth cohort study (Oftedal et al., 2007) used dispersion modelling, while the CCAAPS study used GIS based distances to traffic arteries and a GIS-based regression model (Ryan et al., 2005, 2007). A very recent nested case control study in British Columbia reported increased visits for asthma onset for traffic-related pollutants such as CO, NO, NO_2 and PM_{10} in early childhood including in utero (Clark et al., 2010).

Almost all birth cohort studies listed in Table 3, with the exception of the Oslo birth cohort study, reported increased risk of asthma, asthma incidence, asthma prevalence or persistent wheezing as a key symptom for asthma in early life. Not all effect estimates reached the level of statistical significance, but nonetheless all were positive. Two further cohorts, which recruited the children beyond an age of 4 years found increased risk for asthma incidence (Jerrett et al., 2008; Shima et al., 2003), while a huge population-based study in England found no increase risk of asthma in children (Pujades-Rodríguez et al., 2009).

Besides some inconsistencies we can summarize that living close to busy roads in early life and concomitant exposure to traffic-related air pollutants are independent risk factors for the onset of childhood asthma. Also the summary of more recent reviews are supporting this notion (HEI, 2010; Brabäck and Forsberg, 2009).

The results from the birth cohort studies are rather consistent with the results of prevalence studies on asthma and cohort studies, which recruited the subjects years after birth, although these studies show a larger heterogeneity (HEI, 2010). These cross-sectional studies, mainly performed in school-aged children, are not referenced here because places of exposure other than the indoor home environment might be relevant for exposure when the children are getting older. In light of several experimental studies on traffic-related pollutants and asthma phenotypes (WHO, 2005) and the recent reviews (HEI, 2010; Brabäck and Forsberg, 2009) we conclude that there is suggestive evidence (category B, see Table 1) that there is a causal relationship between traffic-related pollutants and onset of asthma in childhood.

Phthalates

Phthalates, sources and exposure paths

Phthalates are a constituent group of numerous chemicals most commonly used as plasticizers. The incorporation of plasticizers makes polyvinylchloride (PVC) plastics more stable and flexible. These properties of PVC are highly estimated and make PVC available for a broad range of usage such as food wrappers and interior surfaces. The production of plasticizers each year in Western Europe is at about 1 million tonnes of phthalates, where 90% are used as plasticizers for PVC (Plasticisers Information Center, 2007). The most common phthalates are diisononyl phthalate (DiNP), diisodecyl phthalate (DiDP), and di-2-ethyl-hexyl phthalate (DEHP). The typical proportion of DEHP in PVC is approximately 30%. Phthalates may leach, migrate or evaporate from PVC materials into the air, water, soil, dust and food and become an ubiquitous environmental contaminant (Clark et al., 2003). Only a few studies measured phthalates in indoor air or in settled house dust. A Norwegian study found an average concentration of DEHP of 64 μg/100 mg total suspended particulates as the predominant phthalate compound in air-born particles in a few homes of a children cohort. DEHP was also found with an average of 69% as a predominant species in settled dust (Øie et al., 1997). The authors concluded that inhalation of particles bound to DEHP is more important than the exposure via vapour-phase exposure. A further Scandinavian study measured six phthalates in settled dust (Bornehag et al., 2004b) with a median DEHP concentration of 0.77 mg/g dust.

The main route of the exposure to DEHP, or of phthalates in general, is through one's diet (Clark et al., 2003; Wormuth et al., 2006). In particular, fatty foods and even the wrapping of these food items are thought as to be major routes of exposure. However, the proportion of dermal exposure and inhalational exposure in comparison with the route via ingestion is not clearly known yet. Besides this limited knowledge, inhalation via indoor air and/or settled house dust is thought to be minor (Wormuth et al., 2006).

The exposure assessment in epidemiological studies is mainly restricted to collect information on the presence and quality of PVC surfaces indoors. The contribution of the ingestion of phthalates by food items is mostly ignored in epidemiological studies. Even the measurements of phthalates in the indoor air or in settled house dust is restricted to a few homes, which do not allow for the analysing of potential adverse health effects of the occupants.

Epidemiological studies in children

Jaakkola and Knight (2008) published a thorough, systematic review on the potential role of exposure to phthalates from PVC materials in relation to the development of asthma and allergies in children. They searched Medline for such studies published from 1950 through May 2007. They identified seven articles from five epidemiological studies conducted in Scandinavia and Russia (Jaakkola et al., 1999, 2000, 2004; Oie et al., 1999; Bornehag et al., 2004a,b, 2005). The study characteristics and the results are given in Table 1. After this review another paper (Larsson et al., 2008) showed a statistically significant increased risk of incident asthma with PVC flooring. The exposure assessment of all of these studies mostly relied on data about the presence of PVC materials indoors. Only in smaller subsets of subjects phthalates were directly measured indoors. A formal meta-analysis on the combined effect estimates for the presence of PVC materials in the children's indoor homes and the risk of asthma could be performed for four studies in the review by Jaakkola and Knight (2008). They found an adjusted, combined effect estimate for asthma of 1.55 (95%CI, 1.18–2.05). These few children studies have both strengths and weaknesses. One strength is related to the fact that all of these studies have carefully adjusted for a broad range of potentially confounding factors. In addition, the presence of PVC material was assessed by trained investigators in a home inspection. The increased risk for asthma when the exposure to phthalates is combined with the presence of water leakage supports the idea of an underlying causal interrelationship. However, there is also room for complex residual confounding. The use of plastic material might be related to other VOCs, and building dampness might be associated with high levels of different VOCs. Consequently, the observed adverse health effects of phthalates could be due to further exposure to VOCs. The only longitudinal study (Larsson et al., 2008) has a further problem with study validity because the PVC flooring was associated with increased exposure to ETS.

Summary

Epidemiological studies in children showed positive associations between indicators of phthalate exposure at home and the risk of asthma. However, the small numbers of investigations do

Table 3
Association between exposure to traffic-related pollutants at residential address and asthma onset (Birth cohorts only).

Study	Study population	Age	Exposure assessment	Agent	Range of exposure	Outcome	Relative risk	Comments
Gehring et al. (2002a,b)	Birth cohort (GINI and LISA), 1756 children in the city of Munich	1–2 years	Individual exposure estimated from regression models Annual mean at birth	NO_2, $PM_{2.5}$	20–67 μg/m^3, 12–22 μg/m^3	Questionnaire-reported symptoms	Slightly increased OR of non-specific respiratory symptoms, significant only in males	Adjustment for important confounding variables
Morgenstern et al. (2007)	Birth cohort (GINA and LISA), 3577 children from the city of Munich and surrounding area	1–2 years	Individual exposure estimated from regression models and buffer zones variables.	NO_2, $PM_{2.5}$	19–72 μg/m^3 7–15 μg/m^3 Annual mean at birth	Questionnaire-reported symptoms	Distance to nearest main road less than 50 m, OR 1.23 (1.00–1.51) for asthmatic bronchitis Very few children with doctor-diagnosed asthma at this age	Adjustment for important confounding variables
Morgenstern et al. (2008)	Birth cohort (GINA and LISA), 3066 children from the city of Munich and surrounding area	6 years	Individual exposure estimated from regression models and buffer zones variables	NO_2, $PM_{2.5}$	6–74 μg/m^3 19–13 μg/m^3 Average exposure up to 6 years of age.	Questionnaire-reported symptoms Circulating IgE	Distance to nearest main road less than 50 m: OR 1.66 (1.01–2.59) for doctor-diagnosed obstructive bronchitis or asthma OR 1.30 (1.02–1.66) sensitization to pollen	Adjustment for important confounding variables. Blood samples were obtained from 1353 children (an unspecified subset) – the loss in retention rate is not commented
Brauer et al. (2002)	Birth cohort (PIAMA) from the Netherlands, 4,146 children at start, 3,745 at one year and 3,730 at 2 years.	2 years	Individual exposure estimated from regression models	NO_2, $PM_{2.5}$	13–58 μg/m^3 13–25 μg/m^3 Annual mean at birth	Questionnaire-reported symptoms	Slightly but significant increased risk of upper respiratory infections	Adjustment for important confounders.
Brauer et al. (2007)	Birth cohort (PIAMA) 3,538 children (retention 85%) A subgroup of 713 children	4 years	Individual exposure estimated from regression models	NO_2, $PM_{2.5}$	13–58 μg/m^3 13–25 μg/m^3 Annual mean at birth	Questionnaire-reported symptoms Circulating IgE	OR for IQR of PM2.5 1.32 (1.04–1.69) for doctor-diagnosed asthma ever and 1.75 (1.23–2.47) for any sensitization to food allergens	Adjustment for important confounders. High rate of retention High risk children were overrepresented in the IgE screening subgroup Low rate of sensitization to outdoor allergen
Gehring et al. (2009)	Birth cohort (PIAMA) 8 year follow-up of 3,863 chidlren		LUR		NO_2, $PM_{2.5}$ BS	At birth address 19–29 15–18 1.35–1.92	For asthma incidence 1.19 (1.05–1.34) 1.2 (1.10–1.49) 1.21 (1.06–1.38)	After adjustment for study regieons the effect estmates were not statistically significant
Nordling et al. (2008)	Birth cohort (BAMSE) of 4,089 children in Stockholm, Sweden 3,515 replied to questionnaires at 4 years and 2,543 delivered blood samples	4 years	Individual exposure based on atmospheric dispersion model, high resolution	NO_x, Traffic PM	5–49 μg/m^3 1–7 μg/m^3 (P5–P95) Annual mean at birth	Questionnaire-reported symptoms Circulating IgE	OR for 95th % range of NOx 1.60 (1.09–2.36) for persistent wheeze and 1.67 (1.10–2.53) for any sensitization to pollen	Adjustment for important confounders. Analyses based on exposures during 1st year of life Significant difference between extreme percentiles of exposure. Dose-response relations not presented.
Melén et al. (2008)	Case-cohort within the BAMSE birth cohort in Stockholm (a randomly sampled subcohort of 542 nonwheezers and 167 wheezers. In addition 375 wheezers from the original cohort)	4 years	Individual exposure based on atmospheric dispersion model, high resolution	NO_x,		Questionnaire-reported symptoms Circulating IgE	Variants in the GSTP1 and TNF genes modify the association between sensitization and NOx.	

Oftedal et al., 2008	Birth cohort study in Oslo, Norway 2,244 children who lived in Oslo since birth	10–11 years	Individual exposure based on atmospheric dispersion model with contributions from busy roads	NO_2, $PM_{2.5}$ PM_{10}	Mean (IQR) life time estimate 29.0 (19.5) $\mu g/m^3$ NO2 and 12.3 (3.6) $\mu g/m^3$ PM2.5 Smaller ranges compared to Nordling et al	Skin prick test	No association between long-term exposure and sensitization to any allergen (except for *D. farinae*)	Very few children were sensitized to D farinae and the association with traffic exhaust was likely to be caused by confounders
Oftedal et al. (2009)	A cohort of 2,871 children from Oslo	9–10	Retrospective exposure assessment for first year of life by a dispersion model (EPI-SODE)		NO_2 distance to major roads	IQR: 19.6–27.3 $\mu g/m^3$ P25:25 at birth and 16 at 10 years. P75:53 and 34 $\mu g/m^3$ P25–P75	RR for asthmauntil age 10 for NO_2 at first year: 0.81(0.65–1.02) for distance to major roads: 0.98(0.89–1.08) aOR	The effect estimate were adjusted for several confounders including ETS. The dispersion model lead to a rather smoothed exposure assessment.
Ryan et al. (2005)	Birth cohort study (the Cincinnati Childhood Allergy and Air Pollution Study, CCAAPS) – 622 children with at least one allergic parent were enrolled at 6 months	1 year	Individual exposure (distance to various traffic conditions) based on GIS model		Not recorded	Questionnaire-reported wheeze without a cold	Distance to stop-and-go traffic less than 100 m: OR 2.5 (1.15–5.42) for wheezing without a cold No effect from smoking	A small study with limitations in the control of confounding
Ryan et al. (2007)	CCAAPS See above!	1 year	Individual exposure (distance to various traffic conditions) based on GIS model and regression model estimating elemental carbon attributable to traffic	ECAT	0.30 – 0.90 $\mu g/m^3$	Questionnaire-reported wheeze without a cold	Significant exposure-response association between ECAT level and risk of wheeze	The strength of this study is the improved exposure assessment
Clougherty et al. (2007)	Birth cohort – 888 pregnant women were enrolled and the caregivers of 417 children responded to questionnaires after 6–10 years	~7 years	Individual exposure based on a regression model	NO_2	38–85 $\mu g/m^3$	Frequent telephone or face-to-face-interviews In utero exposure for asthma (25 – 75 perc.)	OR for 8 $\mu g/m^3$ increase in NO_2 exposure 1.63 (1.14–2.33) for diagnosed asthma but only in children exposed to violence.	NO_2 was included as a continuous variable. Concentration at the year of diagnosis showed the closest association. Limitations: Low retention rate, reporting bias and potential confounding
Clark et al. (2010)	Birth cohort 37,401 newborns in 1999 and 2000 from southwestern British Columbia nested asthma case (3,482)-control	0–4	high-resolution pollution surface and LUR woodsmoke proximity to major roads	CO, NO, NO_2, PM_{10}, SO_2, black carbon		500–700 21–36 25–37 11–13 4–7 0.9–1.7	1.10(1.06–1.13) 1.08(1.04–1.12) 1.1.2(1.07–1.17) 1.07(1.03-1.12) 1.03(1.02–1.05) 1.14(1.01–1.29)	

not allow for the assessing of a potential publication bias or for the drawing of any conclusion on that. Findings from case studies and epidemiological studies at the workplace supported the notion that increased exposure to phthalates might cause asthma and increase respiratory symptoms. Toxicological studies showed the potential of phthalate species to cause modulation of the immune response (Bornehag and Nanberg, 2010). However, the current epidemiological findings are mostly not based on measurements of indoor phthalates and the most important sources of exposure (food contaminants with phthalates) were ignored. Thus the current study results are not sufficient to draw a final conclusion on the health effects of the exposure to phthalates indoors in relation to the onset or exacerbation of asthma.

We categorize the evidence level to category C: Inadequate/insufficient evidence to infer the presence or absence of a causal relation.

Formaldehyde

Formaldehyde has been one of the most extensively measured indoor chemicals for decades. Considering the strong irritating odour from formaldehyde, the potential health effects from formaldehyde exposure were analysed in several epidemiological studies. A recent review of formaldehyde in the indoor environment (Salthammer et al., 2010) provided a comprehensive overview on substance description, sources, sampling and analysis, indoor guidelines, emission factors, indoor levels, health risk assessment and reduction activities. This review will focus on formaldehyde in dwellings and chidhood asthma.

Sources of formaldehyde in private homes

Elevated indoor formaldehyde concentration might occur if two major source categories are present: (1) combustion processes such as smoking, burning of candles and cooking (IARC, 2006). (2) Emissions from building materials and consumer products, insulating materials like formaldehyde containing foam isolation, and indoor textiles (Dales and Raizenne, 2004). In addition, non-smoking homes emissions from building materials such as pressed wood products, ceilings, flooring, indoor paintings and preservations are the major sources (Dales and Raizenne, 2004).

Several consumer products are also significant sources of formaldehyde. These include household cleaning agents with disinfectant or detergent properties and cosmetics used to preserve the cosmetic composition. Also, glues, paints and lacquers are other important indoor sources of formaldehyde. The specific contribution of each source is difficult to identify. Due to the high reactivity of formaldehyde indoors, the emission of formaldehyde needs to be persistent to make sure that formaldehyde is present for a longer period of time. Several studies have found a strong decline in formaldehyde concentration with time either after redecoration of a home or with increasing age of the potential sources of formaldehyde (Kelly et al., 1999; Haghight and De Bellis, 1998). Although formaldehyde could be measured years after the building of a new or the redecoration of an older home, several studies identified the age of the building or the age of potential sources of formaldehyde as a major determinant of high indoor formaldehyde concentrations (Raw et al., 2004; Clarisse et al., 2003; Gilbert et al., 2006; Guo et al., 2009). In addition, the concentrations for formaldehyde indoors are related to relative indoor humidity rates and temperatures. As other indoor chemicals, formaldehyde concentrations are also related to air exchange rates. The average indoor levels in randomly selected private bedrooms range between 20 and 30 $\mu g/m^3$ (Wieslander et al., 1997a,b; Raw et al., 2004; OQAI, 2006; KUS, 2008) with the exception of an average number of 41.4 $\mu g/m^3$ measured in Finland (Jurvelin et al., 2001) and much higher levels in living rooms in East Asia (Guo et al., 2009).

Exposure routes

Formaldehyde could be absorbed via the inhalation, ingestion and/or dermal routes. The quantification of these specific routes is not well known (CICAD, 2002; EC, 2005).

Formaldehyde and asthma

Due to formaldehyde's strong irritating odour and reactive properties, potential health effects on the sensory system and on the respiratory system were a topic of research. Recent reviews summarize the current understanding of the potential health effects of formaldehyde exposure indoors (IARC, 2006; HEI, 2007). The observational studies consider potential health effects at much lower levels than the levels used for experimental studies. The experimental studies often use concentrations of 1000 $\mu g/m^3$ or more. These concentrations are rarely measured in the indoor environment of private homes. Therefore, the results of these experimental studies can not be transferred to evaluate potential health effects. However, these experimental studies show almost no effect on lung function when exposed to these extremely high concentrations (Lang et al., 2008; Krakowiak et al., 1998). A few observational studies investigated the association between formaldehyde concentrations indoors and respiratory health in children. A very recent systematic review (McGwin et al., 2010) identified seven studies with 5930 participants, 364 of whom had diagnosed asthma. Fixed-effects and random effects models produced OR of 1.03 (95% CI, 1.02–1.04) and of 1.17 (95% CI, 1.01–1.36) for an increment of 10 $\mu g/m^3$ of formaldehyde. These results indicate a significant positive association between formaldehyde exposure and childhood asthma. However, this metaanalysis has some limitations. Out of the seven identified studies, three of them were school-based and four were performed in dwellings. The combined effect estimate for the home setting studies showed increased risks for asthma per 10 $\mu g/m^3$ increase of formaldehyde for the fixed-effect model (OR 1.03 (95% CI, 1.03–1.04)) and the random-effects model (OR 1.10 (95% CI 0.95–1.27)). These positive effect estimates were mainly driven by the study of Garrett et al. (1999), where the authors of the metaanalysis re-calculated an OR of 1.270 (95% CI, 1.040–1.550). This odds ratio was not adjusted. The statement in the original paper by Garrett et al. was: "A higher proportion of asthmatics was seen with higher formaldehyde exposure, with a significant linear trend present ($P = 0.02$). However, after adjusting for parental allergy and parental asthma by logistic regression, the odds ratio for asthma was not significantly different from 1.0" (p. 334 f). Thus, the conclusion of the metaanalysis by McGwin et al. (2010) is overstating the role of formaldehyde exposure in dwellings for childhood asthma. Instead of an uncritical referencing of the results of the systematic review we will describe the very few epidemiological studies on formaldehyde and childhood asthma.

A small case control study compared concentrations of formaldehyde in 88 young asthmatic children below the age of three years with 104 non-asthmatic controls (Rumchev et al., 2002). This study reported a positive association between high concentrations of formaldehyde (>60 $\mu g/m^3$ in the bedroom) with the risk of asthma (OR = 1.4). However, these findings are inconclusive for several reasons. First, one has to take into consideration the small numbers of the study. Second, there could have been potentially confounding emissions of other chemicals from several indoor sources, such as newly used building materials and heating with gas. Finally, one has to take into account the uncertainties involved in diagnosing asthma in children below the age of three years. Another small study included 224 healthy children (aged 6–13 years), and it studied lung function in relation to the concentration of formaldehyde in the bedroom (Franklin et al., 2000).

No association was reported, but the levels of exhaled NO were increased when the children were exposed to levels of formaldehyde above 62 μg/m^3 (OR = 1.8). An additional small study included 148 children from 7 to 14 years of age (Garrett et al., 1999). No association was reported between formaldehyde concentrations in the bedroom (≥20 μg/m^3) and asthma or lung function. While unadjusted associations between peak formaldehyde concentrations measured in several rooms of dwelling and asthma were found, the effect estimates because close to null after adjustment for parental asthma and parental allergy. However, respiratory symptoms were significantly increased when peak formaldehyde levels exceeded 50 μg/m^3. Formaldehyde was also measured in the homes of 298 children of 6–15 years of age (Krzyzanowski et al., 1990). Children exposed to formaldehyde above 41 ppb showed a statistically significant, increased risk for doctor-diagnosed asthma and bronchitis. The adverse health effects were mainly driven by the highest exposed subgroup (above 60 ppb) measured in kitchens. However, the adverse effects might be confounded by ETS, which was correlated with formaldehyde concentrations.

A school-based study included 1993 pupils aged 11–15 years from 10 schools and 34 classes in China (Zhao et al., 2008). Formaldehyde was very low ranging between 1.0–5.0 μg/m^3 (mean 2.3 μg/m^3). No associations were reported for asthma, but for wheeze and daytime and nocturnal attacks for breastlessness.

Summarizing the findings of the observational studies in children's dwellings re-concludes that a convincing association between formaldehyde in dwelling and development of asthma is insufficient (category C: inadequate/insufficient evidence to infer the presence or absence of a causal relation, see Table 1). For other indoor environments like schools the summarizing level of knowledge might be higher.

Polycyclic aromatic hydrocarbons (PAH's)

Sources of exposure to PAHs

Polycyclic aromatic hydrocarbons (PAH's) are a large group of chemicals, which consist of two or more aromatic rings. From the perspective of potential health effects, the particle-bound PAH's might be most important. Specifically, benzo(a)pyrene(BaP) is considered as a representative of the overall exposure to PAH because it represents a large proportion of the total carcinogenic potential (Ohura et al., 2004).

PAH's are ubiquitous environmental pollutants which are mainly emitted by combustion of carbon at high temperatures. PAH's have a variety of indoor sources such as smoking, cooking, cooking or heating on open fires and candle burning (Fromme et al., 1998; Lung et al., 2003; Ohura et al., 2004). In addition, older houses have shown higher concentrations of PAH indoors. In industrialised countries smoking is by far the most important source of PAH's whilst in the developing countries open fires of wood or other materials for cooking or heating purposes are the dominant source of indoor PAH's. This latter point might be what leads to extremely high concentrations (Mitra and Ray, 1995; Gustafson et al., 2008). The emission of PAH's from cooking depends on type of cooking and on the fat content of the food. If the food is fried or generally prepared at high temperatures, then high amounts of PAH's are emitted while cooking (Chang et al., 2006). This might be one reason why high PAH concentrations were measured in Chinese kitchens but also in Asian homes in general.

The main route of exposure is ingestion by food. However, PAH's can also be inhaled (Menzie et al., 1992).

Indoor concentrations of PAH's in private homes

The concentrations of total PAH's indoors range from 5.1 to 39 ng/m^3 (Dubowski and Essary, 1999; Naumova et al., 2002). The levels of BAP are range from 0.01 to 0.65 ng/m^3. Higher concentrations were found in Asian homes potentially due to specific types of Asian cooking. In addition, much higher levels in developing countries are caused by burning of carbonic material in open unvented fire places (Pandit et al., 2001).

Health effects of exposure to PAH's on asthma and allergies

Whilst the carcinogenic and mutagenic effects of PAH's are well established with experimental animal studies and in vitro tests, only a few epidemiological studies have investigated health hazards in relation to PAH exposure in humans. Five epidemiological studies in Teplice/Prague (Czech Republic), Krakow (Poland), New York City (U.S.), and a city in China specifically address the question of health hazards in relation to PAH exposure (Binková et al., 2003; Perera et al., 1998; Choi et al., 2006; Miller et al., 2004; Tang et al., 2008). These studies reported in utero growth retardation, preterm delivery and adverse effects on neurodevelopment. Only one of these studies explored potential health effects on respiratory disease, asthma and allergies (Miller et al., 2004). Within this study children were followed up for two years. The exposure of these children to PAH of those non-smoking mothers was assessed for each subject. The exposure ranged between 0.27 and 36.4 ng/m^3 and showed a statistically significant increase in asthma symptoms during the first two years of life. There are two major concerns with this study result. One is related to the concomitant exposure to ETS, which is a major source of PAH's. In addition, prenatal exposure to ETS is known to cause intrauterine growth retardation and preterm delivery. Since children small for gestational age (SGA) have a higher risk to develop asthma later in life, it is uncertain as to whether the reporting effect is just an effect of PAH's or whether adverse health effects are also partly related to an exposure to ETS. A second concern is related to diagnosing asthma or asthma symptoms during the first two years of life. Summarizing these uncertainties, keeping in mind that only one study specifically reported an association between exposure to PAH indoors and the onset of asthma in children, we evaluate the degree of validity of such an association within the category D.

Benzene

Benzene was classified as a human carcinogen in category 1 in 2004; group 1 in 1987; and category A in 1998 by the European Union, the International Agency for Research on Cancer and the US Environmental Protection Agency. The long lasting suspicions on adverse health effects of benzene exposure led to numerous studies on the exposure to benzene in the workplace setting, in ambient air and indoors. These consisted of animal studies, in vitro tests, occupational exposure studies and a few epidemiological studies.

Indoor sources of benzene concentration

Indoor benzene concentrations are influenced by penetrating benzene from ambient air and by emission of a variety of different indoor sources. The main source of ambient benzene concentrations is traffic-related exhaust which can penetrate indoors and several indoor surfaces might serve as sink. In addition to the traffic-related exhaust, gasoline stations and certain industrial facilities might emit larger amounts of benzene (Jia et al., 2008). Climatic conditions and any resulting active ventilation; the season; and the meteorological conditions, such as inversions; have an additional effect on the concentrations of benzene indoors. Numerous indoor sources of high benzene concentrations have been identified, including: redecoration materials, paint, (Wolkoff, 1995; Srivastava et al., 2000; Brown, 2002) building construction materials, (Hodgson and Levin, 2003), indoor textiles from PVC, nylon and latex backed carpets, and certain furniture and wood panelling (Ezeonu et al., 1994; IEH, 1999; Yu and Crump, 2003). Indoor air benzene concentrations are also influenced by cleaning agents (Kim

et al., 2001), photocopy machines and printers (Lee et al., 2006; Destaillats et al., 2008), and finally tobacco smoking (Singer et al., 2003). In addition to these indoor sources from benzene-emitting materials and from certain human activities, benzene levels could be heavily influenced by the presence of garages that are attached to the living space (Dodson et al., 2008; Ilgen et al., 2001a,b).

The main route of the benzene exposure is the inhalation which is attributable for almost 100% of total benzene exposure in the general population (IEH, 1999).

Indoor levels of benzene concentrations

Mean indoor concentrations of benzene in private homes measured during the last two decades range between 2 and 6 $\mu g/m^3$ (Kotzias et al., 2005; Jia et al., 2008; Sexton et al., 2007). There seems to be a gradient with lower levels in the Nordic European countries compared to the central and southern European countries (Edwards and Jantunen, 2001; Jantunen et al., 1998; Ilgen et al., 2001a; Schneider et al., 2001; Kotzias et al., 2005). Several studies in Asia show much higher levels of indoor concentrations due to kerosin stoves (Pandit et al., 2001) or presumably the building material (Zuraimi et al., 2006).

Benzene concentrations and asthma in children

There are only two studies which look at benzene concentrations indoors in relation to the induction of asthma or pulmonary infections in children. Rumchev et al. (2004a,b) reported an increased risk for doctor-diagnosed asthma starting at 1.9 per 10 $\mu g/m^3$ of benzene. Pulmonary infections were found to be increased (OR = 2.4) in infants' whose homes contained benzene concentrations above 5.6 $\mu g/m^3$ (Diez et al., 2000). Thus far, there also has not been a single study published on potential health effects of benzene on asthma in adults or on whether benzene might exacerbate or cause asthmatic symptoms.

Since the low correlation between adverse health affects and repeated measurements of benzene (Topp et al., 2004) and higher correlations with many other chemicals, the results of the two studies are questionable.

Ultimately, the role of indoor benzene in private homes in relation to asthma in children has to be placed in the lowest evidence level, category D (evidence is suggestive to no causal relation).

Results and discussion: Indoor biocontaminants and childhood asthma

Pets and pet derived allergens

This chapter is based on a systematic review of epidemiological studies published between 2000 and January 2009 (Chen et al., 2010). This review best describes the current understanding of the relationship between pets and asthma in childhood. Allergen exposure is one of the known environmental risk factors associated with the symptoms and the severity of allergy. Avoiding allergens that worsen the symptoms in those who have already developed an allergy is highly recommended for disease management (Custovic et al., 1998). However, whether allergen avoidance prevents or delays the onset of allergy development is still debated. Several randomised control trials on mite allergen avoidance were conducted and the preventive effects were not conclusive (Custovic et al., 2001; Marks et al., 2006; Peat et al., 2004). For pet allergen avoidance, it is difficult to conduct randomized controlled trials. Therefore, the influence of pet allergen exposure on the subsequent development of sensitization or allergic symptoms and diseases relies on the results of observational studies.

The effect of early life cat allergen exposure or cat ownership on the onset of cat sensitization or allergic symptoms and diseases is complex. Conflicting study results with various proposed mechanisms have been published in the past ten years (Almqvist et al., 2003; Celedon et al., 2002; Lau et al., 2005; Platts-Mills et al., 2001). Some studies suggest that cat allergen, like house dust mite allergen, is positively associated with the development of cat sensitization, defined as having increased specific IgE antibody reaction to cat allergen when in contact (Chen et al., 2007; Heissenhuber et al., 2003). Other studies suggest that exposure to high levels of cat allergen may induce immune tolerance (Custovic et al., 2001; Platts-Mills et al., 2001). This involves a modified Th_2 response by increasing the expression of IgG_4 isotype, which is regulated by IL-4 cytokine like IgE. However, it does not trigger clinical immune reactions, and it does not increase the serum IgE level (Aalberse and Schuurman, 2002; Platts-Mills et al., 2001). Nevertheless, these observations have not yet been replicated in other studies (Jarvis et al., 2007; Perzanowski et al., 2008). The interaction between gene and environmental exposure was proposed to be one of the major causes of the inconsistent observations. A recent study showed that cat ownership during infancy substantially increases the risk of eczema within the first year of life in children with the loss-of-function variants in the gene encoding filaggrin (FLG). FLG was shown as a major determinant of eczema development, but not amongst those children without the variants (Bisgaard et al., 2008).

The effect of childhood dog or dog allergen contact is less understood. However, some of the studies have observed a negative association between childhood dog exposure and sensitization to aeroallergens, predominantly outdoor aeroallergens and respiratory symptoms such as wheezing (Almqvist et al., 2003; Litonjua et al., 2002; Remes et al., 2001). It has been proposed that pet-keeping, especially of a dog, may increase the exposure to bacterial components, such as endotoxin, that may enhance children's type 1 lymphocyte (T-helper 1) development and therefore protect them from the development of allergy (Campo et al., 2006; Gern et al., 2004; Lau et al., 2005). However, this speculation could not be verified by some of the studies which attempted to disentangle the protective effect from the simultaneous exposure of dog and endotoxin (Bufford et al., 2008; Chen et al., 2008). Gene-environmental interaction between the genetic variant of CD14, which encode the LPS receptor, and dog ownership on the development of atopic dermatitis has also been reported (Gern et al., 2004); dog ownership was observed to protect children with a TT genotype from developing atopic dermatitis.

As the debate on the appropriateness of pet avoidance goes on, there is a need for a comprehensive systematic review on the association between cat and dog exposure and allergy.

As result of a systematic review of epidemiological studies published between 2000 and January 2009, Chen et al. (2010) summarized that studies have reported contradictory effects of cat and dog exposure on asthma in childhood, resulting in inconsistent recommendations on animal avoidance. Birth-cohort studies indicate that cat and dog exposure in early life does not have an effect on the development of asthma and asthma symptoms. However, cat exposure during infancy seems to increase the risk of cat sensitization while dog exposure during infancy protects children from developing sensitization against inhalant allergens. Studies which followed up school children suggest an inverse association between cat exposure and asthma, but not allergic sensitization. Case–control studies reported inconsistent results. This review shows that cat and dog avoidance cannot prevent allergy. However, this maybe biased due to the nature of the observational studies. Based on the findings of the less biased birth cohort studies one might conclude that pet ownership and also pet-derived allergens do not directly increase the risk of developing asthma in childhood. Before drawing any final conclusions on health consequences of pet ownership one has to consider that exposure to cat and cat allergens is doubtlessly a strong risk factor for developing a specific cat sensitization. Several studies have identified cat sensitization as a strong risk factor

for asthma. However, no paper has shown the relationship between exposure to cat and cat sensitization and asthma in one single study.

Mites and mite allergens

Mite-related allergens are considered one of the major if not the major biogenetic indoor factors supported by strong evidence for a causal relationship with the onset of asthma. From the perspective of potential adverse health effects, the two mite species *dermatophagoides pteronyssinus* and *dermatophagoides farinae* are considered the most important source of mite allergens. Mites feed on human and animal skin scales and require a relative humidity above 60% in their micro-environment. Thus, they have optimal growing conditions in mattresses and pillows which have an abundance of human skin scales and have sufficient humidity caused by the sweating of sleeping people in their sleep. In addition, an upholstery and carpets serve as further micro-environments for mite growth. The main sources of many allergens are mite feces and the total body or fragments of a dead mite (Arlian et al., 1987).

Group 1 allergens such as *D. pteronyssinus 1* (*der p 1*) are glucoproteins with cysteinprothease activity, and they originate from cells lining the intestinal track of the mite (Thomas et al., 1991). Mite allergens are carried on particles that are between 10 and 25 μm. These particles remain airborne only a few minutes and then settle. Therefore the measurements of mite allergens in settled house dust is the preferred matrix to assess the exposure. In particular, mattress dust is important for the assessment of the exposure to mites, because this dust is very close to the breathing zone while sleeping. The dust quality is rather homogeneous and less affected by larger amounts of inorganic materials which were brought in the home, such as sand and stones. The expression of mite concentrations per gram of dust in mattress dust samples is a better indicator than floor dust samples. This is at least the case if the floor dust samples are not sieved. Sieving of floor dust samples may lead to a higher comparability between the different homes and studies. Currently, there is no standardized protocol for dust collection to measure mite concentrations in settled house dust. Studies using different vacuum cleaners with different flows affect the size distribution of the collected particles. In addition, vacuums contain varied filtering materials, such as cellulose filters or nylon filters, which all vary in pore size and which also affect the size distribution of the collected particles. Due to these methodological differences a valid comparison between mite concentrations across different countries and studies. These methodological limitations have been mostly ignored even in review articles which compare mite concentrations across different countries, and this has also an effect on the potential health outcomes. One of the few studies which overcome this lack of standardization in dust sampling protocols and different laboratory methods to measure mite allergen concentration is related to the European Respiratory Health Survey (ECRHS) (Zock et al., 2006). The ECRHS is potentially the only study which allowed for the systematic comparing of mite concentrations across different countries.

Mite concentration across Europe and potential determinants

Within the eight year follow-up of the European Community Respiratory Health Survey in the years 1999–2001 mite concentrations were measured in standardized, collected dust samples from mattresses in 10 European countries (Zock et al., 2006). During home visits, mattress dust samples from 3580 participants were sampled and analysed for *der p 1* and *der f 1*. Overall, in more than 50% of the homes mites could be detected. Concentrations ranged from no or low detectable proportions in the Nordic countries (Island and Sweden) to high detection rates of above 80% in the UK, Belgium and most of the Spanish centres except Albacete. In addition to the geographical variations, further determinants for mite growth could be detected. The geographical variations reflect low winter temperatures with low relative humidity. With a level of relative humidity below 50–60% over a period of more than four weeks *D. pteronyssinus* mites could not survive. Other determinants could be identified for Der p 1, but not for Der f 1, including older mattresses, a lower floor level of bedroom, and dampness (Zock et al., 2006). The explained variance for mite concentrations by several indoor factors was assessed to be approximately a little above 30% (Gross et al., 2000).

Mite allergen exposure and the onset of asthma

Whilst the association between mite allergen exposure and the induction of allergic sensitization to mites on the one hand, and the well-established association between specific allergic sensitization to mites in relation to the onset to asthma on the other, the evidence for mite exposure in relation to asthma has had a mixed result (Sporik et al., 1990; Tovey et al., 2008; Celedon et al., 2007; Lau et al., 2000; Torrent et al., 2007). Out of the three longitudinal study results published during the last two years, two found a positive association between mite exposure and the onset of asthma in childhood (Tovey et al., Celedon et al., 2007). The third study did not find any relationship between home mite allergen concentrations, allergic sensitization or asthma (Torrent et al., 2007). Also, a German birth cohort study did not find a positive association between early exposure to house dust mites and the development of childhood asthma until an age of 13 (Lau et al., 2000). Summarizing these findings there is little evidence for the notion that mite exposure might be directly linked to the onset of asthma. Nevertheless, sufficient evidence comes from an indirect link via an increased risk of allergic sensitization to mites, which is a major predictor for asthma.

The role of mite allergens for causing asthma in childhood and adulthood is by far the best investigated allergen. From observational studies we have some evidence for a causal relationship that exposure to increased levels of mite allergens might contribute to the development of asthma (category B, see Table 1). Nevertheless, avoidance measures to lower the levels of might allergens indoors could not be recommended yet on the bases of the results of randomized clinical trials in asthmatics (Gøtzsche and Johansen, 2008a,b). Despite of the finding of these trials, the potential causal chain from mite allergen exposure to specific allergic sensitization to mite allergens and asthma is much clearer than for many other indoor factors.

Dampness and mould derived components (β-glucans, EPS, endotoxins)

Proportion of children living in damp or mouldy homes

Dampness and mould growth in homes are caused by leakage on roofs or water pipes, condensation due to inadequate ventilation, insufficient isolation of the cellar walls and other failures in the structure of the building. They can also be caused by the occupants' behaviour in relation to insufficient ventilation or the careless use of water. Increased dampness and water damage might also occur as a consequence of accidental failure of water pipes or by floods. The assessment of the level of dampness in home or mould growth in home is commonly based on self reports of occupants. Also, the occurrence of water damage by floods, leakages, accidental failure of water pipes, roof leakages or visible condensation at the window pane might help to assess potential problems with dampness or mould indoors. Inspections of the homes by trained field workers provide a more objective assessment. Also, indoor measurements of relative humidity, temperature, dew point air, and exchange rates might provide more objective data on the state of a home. However, these indoor measurements are mainly restricted to a short period of time which then needs to be repeated in several seasons to allow

the assessment of the difference between ambient and indoor measures. In addition, this allows evaluation of the specific influences of the occupants behaviour such as cooking, washing, ironing or taking showers, which is considered to have strong influences on relative humidity indoors apart of the ventilation activities. The repeated measurements of dampness-related factors or repeated inspections are time consuming and expansive. Therefore, the most common approach to assess potential problems with dampness and mould is related to self-reported dampness and visible moulds in the home. The EUROSTAT database, which covered a European population of several thousand subjects across the continent, assessed the proportion of the total population living in homes with self-reported problems of damp in the years 1995–2001 to 10–50% (EUROSTAT, 2007). However, there are huge regional differences between the proportions of damp homes across Europe. Within the period of 1995–2001 there seems to be a decrease in the proportion of damp homes in more or less all countries. However, this should not allow one to take this issue any less seriously than before.

Since the data of the EUROSTAT survey refers to households, these data could be used as a surrogate for the proportion of exposed children across Europe. That means that 10–50% of our children, depending on the country, are growing up in damp homes. The damp homes are considered as being a higher risk for growing moulds and other damp-dependent bacteria and bio-agents. Yet, not all homes that are reported as being damp are growing mould. In addition to the induction of growth of several microbial species, an increased dampness might the influence the chemical reaction between emitted chemicals from building materials or textiles of furnishing. On the other hand, some microbes' growth which are positively affected by increased dampness might be involved in the degradation of chemicals.

Dampness and visible mould in homes in relation to respiratory health including asthma

There are a large number of epidemiological studies on dampness and visible moulds in homes in relation to the respiratory health. The most recent summaries are based on a well-performed meta analysis (Fisk et al., 2007), a WHO report (WHO, 2007) and the WHO summary on a working group meeting in 2007 on dampness and moisture and associated biological pollutants (WHO, 2007). The most recent WHO report (2007) summarized the health risk evaluation for living in damp or mouldy homes quality.

Apart from the qualitative assessment of the WHO report (2007), the formulized meta analyses by Fisk et al. (2007) allowed an assessment of the quantitative relationship between living in damp or mouldy homes and several respiratory health outcomes. The following respiratory symptoms were commonly used as the adverse respiratory health indicators: cough, nocturnal cough, rhinitis, hoarseness, wheezing and asthma (Bornehag et al., 2001, 2004a,b; IOM, 2004). For this review 'asthma development' is the most important outcome. Also, in a cross-sectional study design life-time and current asthma will be used as outcome of interest.

Fisk et al., reported an increase for several asthma related diagnosis for 30-50% for those subjects who are living in damp or mouldy homes (Table 4). This increase was not specific for children, but combined adult and children studies. However, the association for wheezing and the combined effect estimate for wheezing were higher for the children's study (adjusted odds ratio 1.53 (95% CI 1.39–1.68) in comparison to the 5 adult studies (adjusted odds ratio 1.39 (95% 1.04–1.85). Therefore one might conclude that the reported effect estimates for children might be even higher than the reported overall estimate on asthma of 30–50%. In addition to the specific effects for asthma other respiratory health symptoms of the upper airways and cough was reported by Fisk et al. (2007, see Table 3).

A few more studies which were published after the meta analyses showed a statistically significant increased risk for new asthma among children in a large Finish study (Pekkanen et al., 2007; Antova et al., 2008; Iossifova et al., 2009; Dong et al., 2008; Karvonen et al., 2009), see also Table 2. A recent school based study also showed that exposure to dampness in schools is related to adverse effects on several respiratory symptoms including asthma (Kim et al., 2007).

In addition to these recent observational studies, a few intervention studies showed a positive effect of removal of the source of moisture and removal of mould on the occupants of respiratory health (Meklin et al., 2005). The studies have also shown that some of the adverse health effects might be reversible. This is at least the case for the reported respiratory symptoms.

Meta-analyses for adults in a large European study have consistently shown increased risk for asthma in adults when living in damp or mouldy homes (Fisk et al., 2007; Zock et al., 2002).

In summary, living in a damp or mouldy environment is of increased risk for a number of short-term and long-term adverse health effects including asthma development in children. The most recent WHO review (2009) concluded there is sufficient evidence of association between asthma development and indoor dampness-related agents. This evaluation goes beyond the previous assessment by IOM (2004), which summarized the level of evidence as limited or suggestive evidence of association". The reasons for the revised evaluation by WHO, 2009, were related to more recent studies with improved quality (see Table 2). However, the mechanisms and the underlying specific agents which cause these effects, and might play a central role for the development of asthma, is less investigated. In the following chapters we will review the few studies which specifically looked at damp related bio-agents and their role for the development of asthma in children.

Microbial components and asthma

Increased dampness stimulates growth of various fungi, bacteria, amoebae, house dust mites and other biological agents that proliferate due to the increasingly favourable environement made by the presence of water. In addition, chemical pollutants which might be products of microbial growth or of the degradation of chemicals by microbes might also be influenced by increased moisture. Microbial exposures can be characterized by cultural methods and by using the common cellular components of microbial cells as their surrogate. Endotoxin, the component of the wall of gram negative bacteria is commonly used as a surrogate for microbial exposure. Endotoxin represents a very bio-active component with a lot of stimulating properties (Douwes et al., 2000). Other important bio-active components are the (1,3) and (1,6-β-glucans), which are also cell-wall components, but indicative of fungal growth. Both components have inflammatory properties including an irritation of the airways and immune-stimulating characteristics. Other components such as gram positive bacteria or specific species of moulds or bacteria have been less investigated. Thus their role in potentially causing adverse health effect is mostly unknown.

Epidemiological studies on microbial components have been mostly limited to studies on endotoxin and ergosterol; a few have also included exposure assessment for β-glucans and fewer for myco-toxins. This is in part because of the difficulties in the measurements and exposure assessment of these dampness-related agents. Newly developed PCR techniques will allow an improved exposure assessment, and more results are expected in the near future.

Several studies investigated the associations between indoor-dampness-related agents and asthma-like-outcomes (see Table 5). The results are not conclusive.

Some studies have shown that visible mould in homes increases the risk of doctor-diagnosed asthma and wheezing in children

Table 4
Studies on dampness or visible moulds and asthma in children.

Study country	Subjects	Age	Design	Exposure assessment	Outcome	Results
Fisk et al. (2007)	Children of 14 studies	1–14 years	Meta-analyses	Water leakage Floor moisture Visible dampness Condensation Mould odor	Asthma Asthma symptoms Respiratory symptoms	See Table 3
Studies published beyond the meta-analysis by Fisk et al. (2007)						
Jaakkola et al. (2005), Finland	2568	1–7 years	cohort	self-reported mold odor, visible mold moisture, water damage	Asthma	Apart from increased risk for new onset of asthma for mold odor (2.4(1.1–5.6) no other damp/mold indicator was associated with asthma
		6 years. follow up				
Pekkanen et al. (2007), Finland	121 asthma cases	12–84 months	Case control	inspection of the home	Asthma	Risk of asthma increased with severity of moisture damage (aOR 2.11(1.06–4.21), aOR 2.46(1.09–5.55) for minor and major damage) and presence of visible moulds/mold spots in main living area, but not in other areas
	241 controls			living in current home most of their life (75%)	Asthma symptoms	
Antova et al. (2008), U.S., Russia, Europe	58000 from 12 studies in U.S., Russia and Europe	6–12 years	cross-sectional	self-reported question on visible mould and dampness in home	Asthma	Visible mould was associated with nocturnal cough (1.30(1.22–1.39), morning cough (1.50(1.31–1.73), wheeze (1.43(1.36–1.49), hay fever (1.35(1.18–1.53) and asthma (1.35(1.20–1.51).
					Asthma symptoms Hay fever	
Dong et al. (2008), China	3945 China	1–6 years	cross-sectional	self-reported visible moulds at home	Asthma	Visible moulds was associated with cough (1.33(1.01–1.76), doctor diagnosed asthma (1.56(1.13–2.16), current asthma (1.89(1.22–2.94), current wheeze (2.07(1.56–2.75) and allergic rhinitis (1.20(0.72–1.99).
					Asthma symptoms Allergic rhinitis	
Iossifova et al. (2009), U.S.	483	3 years	birth cohort	inspection	Asthma-index	Visible mold was associated with an asthma predictive index (7.1(2.2–12.6).
Karvonen et al. (2009), Finland	396	18 months	birth cohort	inspection	Asthma- symptoms	Visible mold in main living area and moisture damage in the kitchen were associated with increased risk for doctor diagnosed wheeze (3.92 (1.54–10.00) and (3.89(1.39–10.87) no association with cough and respiratory infection

Table 5
Exposure to microbial agents and asthma and asthma-symptoms in children.

Study	Subjects	Age	Design	Exposure assessment	Agent	Outcome	Results
Park et al. (2001), U.S.	499 infants with parental allergy		cohort	floor dust	endotoxin	wheeze	increased risk for a wheeze (1.33 (0.99–1.79)) and repeated wheeze (1.55 (1.00–2.42))
Belanger et al. (2003), U.S.	849 infants with siblings with asthma	1–12 months	birth cohort		fungal colonies	wheeze	increased wheeze (1.23 (1.01–1.49) if mother has asthma and 1.10 (0.99–1.23) without asthmatic mother
van Strien et al. (2004a,b)	241 farm children 311 non-farm children	6–14 years	cross-sectional	measurements	muramic acid	doctor diagnosed asthma wheeze	no statistical significance, association between asthma and wheeze with the measured exposure
Rural areas in Europe							
Douwes et al. (2006), NL	696	1–4 years	birth cohort	measurements in settled floor dust	EPS	Doctor diagnosed asthma	exposure to EPS, glucans and endotoxin, lowered the risk for asthma (0.4, 0.7, 0.4) and wheeze (0.4, 0.4, 0.7)
	(PIAMA)				glucans endotoxin	persistent wheeze	
Hyvärinen et al. (2006), Finland	36 asthma cases 36 controls	1–7 years	case–control	measurements	ergosterol bacteria	asthma	statistically significant, no association with asthma
Dales et al. (2006)	332 children				endotoxin	number wheezing day	Increased wheeze with increased exposure to endotoxin
Kim et al. (2007), Sweden	1014	school age	cross-sectional		Bacteria MVOC	doctor diagnosed asthma	increased risk for asthma, when MVOC increases
Iossifova et al. (2009), U.S.	483	3 years	birth cohort	floor dust sampling at age 8 months inspection of the home	glucan endotoxin	asthma-index	Exposure to high glucans showed decreased risk for asthma-predictive index (API) (0.6 (0.2–1.6)) exposure to endotoxin was statistically not significant associated with API
Iossifova et al. (2007), U.S.	547	11–18 months	birth cohort	floor dust was sampled	glucan endotoxin	wheeze allergic sensitization	Exposure to high glucan concentrations was associated with a reduced risk for recurrent wheeze (0.39 (0.16–0.93)) and allergic sensitization

(IOM, 2004; Pekkanen et al., 2007; Antova et al., 2008; Dong et al., 2008; Iossifova et al., 2009; Karvonen et al., 2009). A birth cohort study in the US concluded that one-year-old children of asthmatic and allergic mothers who were exposed to high levels of *Penicillium*, a common species of mould, are at a significantly higher risk of develping wheezing and persistent coughing (Gent et al., 2002). Another US study showed that exposure to dust born *Aspergillus, Alternaria* and *Aureobasidium* at 3 months of age contributes to the development of doctor-diagnosed allergic rhinitis within the first 5 years of life (Stark et al., 2005).

In addition to visible mould and specific mould species, some studies measured bio-components of mould, such as (1,3)-ß-D-glucan and Extracellular Polysaccharides (EPS), as surrogates for mould exposure (Gehring et al., 2007; Giovannangelo et al., 2007; Iossifova et al., 2007). (1,3)-ß-D-glucan are non-allergenic, water-insoluble, structural cell-wall components of most fungi, which may also be collected from plant materials, including pollen and cellulose, and soil bacteria. Therefore the measured glucan may overestimate the level of mould exposure. Fungal Extracellular Polysaccharides (EPS) are stable carbohydrates secreted or shed during fungal growth, and they have antigenic specificity at the genus level. In contrast to the findings on visible mould and measured specific mould species, cohort and birth cohort studies showed that exposure to (1,3)-ß-D-glucan and EPS decreases the risk of developing wheezing symptoms and parental-reported, doctor-diagnosed asthma in children (Douwes et al., 2006; Iossifova et al., 2007, 2009). In addition, one case–control study reported that elevated levels of (1,3)-ß-D-glucan and EPS exposure from mattress dust is associated with a lower prevalence of allergic sensitisation in 2- to 4-year-old children (Gehring et al., 2007). However, the mechanism of these inverse effects is not yet understood. Different ways of assessing mould exposure can be one of the reasons for the conflicting study results. Haas et al., reported that visible mould growth was significantly correlated with the concentration of fungal spores (Haas et al., 2007). A similar observation was made for the comparison of airborne ergosterol and (1,3)-ß-D-glucan in relation to visible mould (Foto et al., 2004). In contrast to the latter, a US cohort study did not observe a correlation between (1,3)-ß-D-glucan exposure and visible mould (Iossifova et al., 2007, 2009).

Furthermore, the period during which one is exposed to mould or mould components also showed a difference impacts on allergic health outcomes (Sahakian et al., 2008). The immune response of newborns is dominated by Th2 cells and a shift to Th1-mediated immune response happens during early childhood. It has been suspected that (1,3)-ß-D-glucan and EPS may have a similar impact on the development of an infant's immune system as early endotoxin exposure (Schram-Bijkerk et al., 2005; Schaub et al., 2006; Iossifova et al., 2007).

In support of the 'hygiene hypothesis' (Strachan, 1989; Strachan and Carey, 1995), previous studies showed that children growing up on farms have a lower prevalence of hay fever and atopic sensitisation. It is assumed that the high endotoxin exposure in farming environment could affect the development of children's immune system early in life (Portengen et al., 2002). Other studies reported that exposure to higher levels of indoor endotoxin is associated with a decreased risk of allergic sensitisation and disorders in children of preschool and school age (Gereda et al., 2000; Braun-Fahrländer et al., 2002; Gehring et al., 2002a,b).

Adult studies provided evidence for an agent specific effect on asthma (Sahakian et al., 2008). In contrast, several of the studies in children and infants reported protective effects. This duality might be related to different levels of exposure, different vulnerabilities during specific time windows of exposure, a lack of additional exposures at workplace in the children studies and many more influencing factors.

In summary, the adverse health effects including asthma development for living in damp or mouldy home seems to be consistently clear. A few intervention studies on removing moulds or reducing dampness showed beneficial effects on respiratory health. However, fewer observational studies have attempted to clarify the influence of damp-related agents such as fungal components, glucans, EPS, endotoxin and mycotoxins. These studies did not report consistent findings, which might be related to difficulties in exposure assessment and varying roles at different times in life. Despite these numerous inconsistencies we categorize the level of knowledge for living in damp or moldy homes and damp and mold-related indoor factors in association with childhood asthma as category b (see Table 1).

Conclusions

Infants and children spend more than 80% of their time indoors, and thus most of the air they breath is indoor air. In spite of the enormous impact of indoor air, epidemiological methods have not been extensively used to conduct investigations on its adverse health effects, which might be related to a broad spectrum of indoor factors. More specifically, only a few studies have investigated the role of indoor factors on the onset of asthma in childhood. Nevertheless, the published study results allow drawing valid conclusions for preventive measures to avoid asthma in childhood so far.

Conclusions for preventive measures against asthma onset in childhood

As preventive measures three actions might be considered:

(i) Avoiding or reducing the source of an indoor factor that might have adverse effects on the onset of asthma
(ii) Reducing the concentration of, or diluting, the indoor air pollutants through increased ventilation
(iii) Increasing air exchange rates or removal of dust.

In the following we will conclude by suggesting a few avoidance actions of major sources of indoor air pollutants based on the results of the reviewed epidemiological studies.

Environmental tobacco smoke (ETS)

Since exposure to ETS is a likely cause for the onset of asthma in childhood, we conclude that there is a strong need to prevent infants and children from breathing air which is contaminated with tobacco smoke. There is no need for more research. The evidence of an adverse health effect of the exposure to ETS is sufficiently strong to propose such actions.

Cleaning activities

In terms of avoiding actions for asthma onset no specific conclusions could be drawn in relation to cleaning activities, including the use of indoor cleaning chemical agents. More studies are required to better understand the adverse health effects of the use of chemical agents.

Emissions of gas cooking

Although the published findings of epidemiological studies do not show sufficient evidence for a causal relationship between the use of gas for cooking or heating purposes, we conclude that extensive ventilation is needed while cooking with gas. This conclusion is drawn as a precautionary principle.

Renovation and re-decoration activities

There are too many uncertainties to draw a conclusion that renovation and decoration activities, and accordingly emitted volatile organic compounds, might cause asthma in childhood. However, this source has not been investigated extensively and more research is needed. Independent from the need for these future research studies, we can still conclude that there is a need for extensive ventilation for several months after renovation and redecoration. This conclusion is more or less derived as a precautionary principle.

Traffic related pollutants, which penetrate indoors

Despite the suggestive evidence that exposure to traffic-related pollutants that may penetrate indoors might cause asthma in children, it is not easy to draw a strong conclusion for avoidance measures. There are several reasons for living close to freeways and major roads, including cheap rents. Thus, concluding that moving to a cleaner area is recommended could be impractical because some families do not have the capability to move to cleaner environments. One recommendation could be that ventilating the backyards before or after rush hours might help. Still, the effect is probably not very strong.

Indoor chemicals with multiple sources

There is no, or very little, evidence that other indoor chemicals such as phthalates, polycyclic aromatic hydrocarbons and benzene might cause asthma in childhood. However, a reduction of the air concentrations by sufficient air exchange rates and active ventilation is recommended. This recommendation is based on other potential adverse health effects than asthma onset, and it is considered a precautionary principle. For the same reason it is recommended to use low emitting materials, which is more efficient to reduce VOCs concentrations than increasing ventilation.

Pets and pet derived allergens

After an extensive systematic review of the current knowledge, we cannot recommend pet avoidance as a preventive measure for asthma. Further research is also not needed on the topic. A huge number of epidemiological studies have already investigated the potential association between pet ownership and pet derived allergens in relation to asthma onset, and they fail to show any consistent association.

Mite allergens

The role of mite allergen exposure for causing asthma in childhood is by far the best investigated allergen. Several observational studies show a strong association between mite allergen exposure and the onset of asthma. Since interventional studies – mostly by mattress covers – do not show any preventive effect for asthma, we cannot recommend avoidance measure against mite allergen exposure to prevent asthma. Since measures to reduce mite growth such as reducing dampness by ventilation in particular during cold and dry season are similar to reduce other indoor exposures, sufficient ventilation is recommended.

Dampness and mould derived components

The consistent reportings of several epidemiological findings on the adverse health effects of living in damp homes or those with visible moulds lead us to conclude that the source of indoor moulds and increased dampness need to be changed. Such sources include water damage, insufficient ventilation and building construction. In terms of the specific agent which might cause asthma, more research is needed to better understand which species and which agents might cause asthma or other health problems.

In summary we conclude that it is time to act against exposure to environmental tobacco smoke, water damage and insufficient ventilation in order to prevent asthma onset in childhood. As a precautionary principle, more attention has to be paid for a general increased air exchange rate and active ventilation. More research is needed for a better understanding of potential adverse health effects on the frequent use of cleaning chemical agents, on emissions from paintings, on floorings and other building materials and finally on damp related mould components.

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