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Combined or multiple exposure to health stressors in indoor built environments

An evidence-based review prepared for the WHO training workshop " Multiple environmental exposures and risks "

**16-18 October 2013
Bonn, Germany**

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ABSTRACT

Millions of citizens within the WHO European Region spend approximately 90% of their time indoors: in their homes (2/3 of this time), workplaces, schools, and public spaces. Despite undeniable improvements in the quality of indoor environments in the last twenty years, a range of health risks still exists, such as indoor air pollution, injury risks, noise, humidity, mould growth, inadequate indoor temperature, lack of hygiene and sanitation equipment, and crowding. Many of these risks are either directly or indirectly related to the quality of the building. Furthermore, problems with building quality disproportionally affect vulnerable population groups in terms of socioeconomic status or class age.

Despite the scientific progress in understanding the connection between indoor environments and health, evidence is often restricted to categorical studies targeting specific health risks and/or outcomes; much less evidence is available regarding the combined or multiple exposure to risk factors.

This report aims to explore and shed light on the links between different exposure stressors and modifiers people confront in residential dwellings, day care centers, schools and kindergartens. It summarizes a systematic review of literature and project reports presenting evidence on multiple or combined risk exposure in indoor environments, covering the range of health risks encountered.

Table of contents

Executive Summary

The objective of this study was to undertake, summarize, and present a systematic review of literature and project reports (after 2005, English only) presenting evidence on multiple or combined risk exposure in indoor built environments. The review covered safety threats and injuries, indoor air pollution, use of household chemicals, noise, damp and mould, thermal conditions, crowding, inadequate hygiene standards, and harmful building and equipment/furnishing materials. In terms of indoor settings the review covered: (a) residential buildings, as well as (b) day care and school settings. Occupational and medical settings were excluded. In addition to searching the published literature through a number of international online databases (Scopus, PubMed, Medline, Google Scholar), results, reports, and databases on the subject that are not necessarily available through journal databases were included to the extent possible (EnVIE, LARES, INTARESE, HEIMTSA, INTERA, SILC, EQLS etc.). The PRISMA methodology was followed for the systematic review in view of the large number of entries found in these databases and the need for a well-targeted methodology to ensure identified publications are relevant to the task. There is a lot of evidence and studies on non-occupational indoor risks. However, the focus is mainly on health outcomes from single stressor exposure and often multiple risks are related to confounding in epidemiological studies. As a consequence, these studies—although rich in data—do not necessarily provide a good overview of multiple exposure to these health stressors and their association to adverse health outcomes *per se*. In fact, aside from simple additivity of effects and some specific cases of exposure to at most two simultaneous stressors, which may enhance or counteract each other, there is limited actual evidence available on health effects of co-exposure to multiple stressors. The summary report describes the main findings of the studies and projects on multiple exposure in indoor settings, separated by the three settings (home, school, day care). Aditionally, the report indicates the most frequent combinations of risk exposure and reveals the impact of combined/multiple exposure on risk ratios for reported outcomes when data on the latter are available.

A general overview on multiple exposure in built environments can be made for private homes. International databases provide strong evidence that residential buildings are often affected by more than just one environmental problem, indicating that multiple and combined exposure to potential health stressors is rather frequent. For example, data from the EU-SILC (European Union Statistics on Income and Living Conditions) for 2011 show that 0.3% (equaling about 1.5 million individuals) of the EU population are considered to live in "deprived" housing with exposure to four risk factors. In the Eastern part of the European Union (EU), this percentage is as high as 1.3%. A much larger percentage of the population (0.9% for the whole EU and 3.7% for the Eastern EU members) lives in housing affected by three risk factors. Similar problems exist in relation to the housing environment – 3.6% of all EU households reported being affected in parallel by noise, fear of crime, and outdoor environmental pollution.

Recent data compiled by the European Quality of Life Survey (EQLS) 2012 shows that 8.8% of the surveyed population reported having at least four out of eight potential housing problems. Again, Southeastern European countries perform much worse (highest percentages of above 18% are evident for Romania and Bulgaria, and beyond 25% for Turkey), and being at risk of poverty significantly increases the risk of being exposed to such inadequate housing conditions (16.3%). Unsurprisingly, exposure to multiple housing problems is associated with a decreased health status.

Finally, the WHO LARES survey enables a detailed insight into the prevalence of, and the health status associated with multiple housing exposure based on data from eight European

cities. A multiple exposure score covering 14 housing risk factors indicates that 16.5% of the population is exposed to at least five risk factors in parallel. With a rising number of housing risks, the self-reported health status of the residing population decreases, while the reporting of mental health symptoms, allergic symptoms and cardiovascular and respiratory diseases increases. Similarly, dwellings identified as having an increased number of environmental and structural hazards are associated with a greater incidence of home injuries.

The data from these three surveys provide convincing evidence that: multiple environmental exposure in residential housing is widespread throughout Europe; it especially affects the more vulnerable population groups; and that it is significantly associated with poor health outcomes. Unfortunately, similar databases were not identified for schools, kindergartens or day care centers.

Regarding the results of the literature review, three key findings can be identified:

The most frequent combinations of risk exposure in indoor environments, according to the literature reviewed, pertain to chemical mixtures of pollutants that are almost ubiquitous in this setting. Such chemicals include: carbonyls (e.g. formaldehyde and to a lesser extent acetaldehyde), volatile organic compounds such as phenolic compounds (e.g. benzene, toluene, ethylbenzene and xylenes, the so-called BTEX mixture) and terpenes, particulate matter, and polyaromatic hydrocarbons, with the latter being known as carcinogens. Over the last decade a number of studies revealed the existence of a significant number of phthalates and brominated flame retardants in indoor air. These substances, characterized as endocrine disruptors, have been associated with emissions from building materials such as carpet lining and vinyl flooring, as well as emissions from consumer products — electronic goods and other inflammation-prone electric equipment – found at almost all residences, schools/kindergartens, and day care facilities. For the chemical mixtures identified as most frequent in indoor space, additivity of effects was observed at concentrations encountered usually in non-occupational settings.

The second most frequent combination of stressors includes the simultaneous and multiple exposure to air pollutant mixtures and biological stressors, such as mould/dampness and mite allergens, or physical stressors such as noise and thermal (dis)comfort. A closer look at the related literature reveals that one can identify significant physicochemical and mechanical interactions mutually reinforcing the presence of these health stressors in the indoor environment. For example, cold homes have a higher risk of dampness and mould. The presence of dampness and mould in the walls of a residence tends to enhance wall brittleness and, thus, contributes to the indoor levels of ultrafine and fine particulate matter. Older, more brittle walls would be expected to release volatile and semi-volatile organic compounds at a higher rate than when the house was initially built; at the same time, adsorption of such compounds onto the walls increases due to the higher porosity and active surface of the wall material. More porous wall material, in turn, provides a very good substrate for mould growth in case of high indoor humidity and dampness levels. The epidemiological studies analysing health effects of combined exposure to indoor chemicals (e.g. formaldehyde) and mould or mite allergens have demonstrated that the actual effect on adverse health outcomes is more pronounced than the effect observed after exposure to single pollutants.

The third most frequent stressor combination concerns the multiple presence of and interaction between physical and biological stressors, such as noise, thermal conditions and/or mould, and adverse indoor conditions such as crowding or substandard hygiene. In this particular case, socioeconomic differences play an important role in determining the actual exposure to the above stressor combination and, thus, to the consequent adverse health effects. In the light of the current financial crisis and the increasing immigration pressure in Europe, the connection between socioeconomic status of households and

combined exposure to health stressors in the indoor environment is likely to escalate if proper attention is not paid to this phenomenon.

Combined exposure to chemical and biological agents in the indoor environment may result in increasing risk of adverse health effects. This is depicted in the case of co-exposure to chemicals from carpeting and mould which has been shown to produce adverse health effects beyond additivity. Moreover, the observational data suggest the existence of a synergistic mechanism or enchanced physiological susceptibility of adults to biological agents when co-exposed to phthalates and other organic chemicals – which represent compounds emitted from building materials and consumer goods frequently used in residential indoor settings. Children living in houses regularly cleaned with bleach and consequently exposed to volatile chlorination products were found to be less likely to experience asthma and be sensitized to indoor aeroallergens, especially house dust mite. These protective effects were independent of gender, ethnicity, previous respiratory infections, total serum immunoglobulin E level, and family history of allergic diseases. Of great interest is the finding that the above protective effects were nullified by parental smoking, which also interacted with the use of bleach to increase the risk of recurrent bronchitis. Thus, cleaning with chlorine bleach appears to protect children from the risks of asthma and sensitization to indoor allergens. However, during co-exposure to second-hand smoke the risk of recurrent bronchitis increases.

Selected examples are presented in this report in more detail, indicating the health impact of multiple exposure and providing thorough data on exposure levels and health effects. These include the following studies: a study of combined exposure to carbonyls (e.g. formaldehyde) and allergens from pets in France; a study from Belgium analysing the effects from combined exposure to bleach and other indoor stressors (e.g. second-hand smoke) have on children; a study done in France on air pollution and acrolein exposure regarding its effect on non-atopic asthma and other respiratory health outcomes in schoolchildren; a study of children'schildren's exposure to fungi and actinomycetes present in farming and non-farming environments (children's bedrooms and cowsheds) and the comparative assessment of the respective adverse health outcome; an EU-wide study of combined exposure to mixtures of almost ubiquitous indoor volatile organic compounds across different types of indoor settings and the determination of the related health outcomes; and, finally, a study of multiple exposure to air pollutants in Austrian schools and its effect on lung function among schoolchildren.

During the review of the identified literature, special attention was paid to potential indications of inequalities and socioeconomic and demographic disparities in relation to multiple exposures. The report includes a short section where these findings are summarized, indicating the potential relevance of high multiple exposure in disadvantaged groups. Moreover, socioeconomic and demographic inequalities regarding exposure to environmental hazards exist across Europe. Two aspects of housing inequality have been distinguished from a public health perspective: inequalities related to the basic needs for water and equipment availability for drinking, cooking, and hygiene, and inequalities related to overcrowding, dampness, and the capacity to keep the home warm or cool. The main health effect associated with water and sanitation indicators is infectious disease, while those associated with the latter indicators are allergic and respiratory or cardiovascular diseases. The reviewed data provide strong evidence that non-sanitary housing inequalities – overcrowding, dampness, and thermal comfort –are prevalent in almost every country. Low-income populations, in particular low-income single-parent households, are most affected across all indicators, leading to higher exposure levels and, thus, increased likelihood of multiple exposures. Social inequalities in second-hand smoke exposure at home exist with higher exposure among socially disadvantaged groups, characterized by low self-assessed social position, difficulty paying bills, and unemployment. Further, a correlation between

relative poverty and exposure to high traffic noise has been established based on actual field data in several EU countries. Finally, children from highly educated parents would seem to be protected from non-atopic respiratory symptoms, an observation that is largely explained by the lower rate of household smoking and higher rate of breastfeeding.

Overall, this review study shows that a significant amount of evidence exists on human exposure to multiple health stressors in non-occupational indoor settings, such as dwellings, schools, kindergartens, and day care facilities. Less literature is available on the assessment of adverse health outcomes associated with combined exposure to several health stressors or types of stressors. The available evidence indicates that the relationship between indoor environment stressors and public health needs to be addressed by a new paradigm focusing not on the risks of individual stressors, but rather on the actual modification of the reckoned risk. This risk is a consequence of combined or multiple exposure to the stressors characteristic of each type of indoor environment, taking into account socioeconomic and demographic differences.

1. Introduction

1.1 Scope of work

Millions of Europeans in modern society spend approximately 90% of their time indoors: in their homes, workplaces, schools, and public spaces. It is estimated that approximately 2/3 of this time is spent at home. For many years, the housing environment has been acknowledged as one of the main settings affecting human health. Indoor air quality, home safety, noise, humidity, mould growth, indoor temperature, volatile organic compounds (VOC), lack of hygiene and sanitation equipment, and crowding are some of the most relevant health threats possible to be found in dwellings. Many health problems are either directly or indirectly related to the quality of the building, due to construction materials used and the equipment installed, or the size or design of the individual dwellings. Problems with building quality disproportionally affect vulnerable population groups in terms of socioeconomic status (SES) or class age.

Despite undeniable improvements in the quality of indoor environments in the last twenty years, there are still many adverse health outcomes associated with these environments. This has become more evident due to rapid improvement in our understanding of health effects related to the indoor environment over the past decade. In previous years, discussions of indoor environmental quality (IEQ) focused on indoor air constituents (primarily particles, bioaerosols, and chemicals), and comfort factors (temperature, air flow, and humidity). However, despite the scientific progress in understanding the connection between indoor environments and health, such efforts still tend to be categorical: studies frequently tend to address a narrow range of both potential health stressors and associated health concerns, such as VOC exposure, respiratory problems or injury. Only recently has the scientific community begun to look at the association between the built environment and human health as a complex interaction between building occupants (who they are and what they do) and an array of physical, chemical, biological, and socioeconomic factors. This new integrated vision should guide the development of "primary preventive" measures related to housing construction, renovation, use and maintenance, which can promote better overall health and finally support the development of international guidance on "healthy housing" to *help prevent a wide range of diseases and unintentional injuries that can be effectively addressed through better housing* (as stated by an international consultation of 40 experts from 18 countries hosted by the World Health Organization (WHO) in Geneva in October 2010 (WHO, 2010)).

In this context, this report aims to explore and emphasize the links between different exposure stressors and modifiers people are confronting in the indoor built environment. Accordingly, the report undertakes, summarizes, and presents a systematic review of literature and project reports presenting evidence on multiple or combined risk exposure in indoor built environments. The review covers safety threats and injuries, indoor air pollution, use of household chemicals, noise, damp and mould, thermal conditions, crowding, inadequate hygiene standards, and harmful building and equipment/furnishing materials. For clarity reasons regarding the different challenges encountered in different indoor settings, the results of the systematic review are separated by environment type, referring to: (a) residential buildings; (b) day care; and (c) school and kindergarten settings. The review process also covered relevant reports that are not necessarily available through journal databases, in order to include recent evidence that might not be published in international literature.

In order to give a better overview of the impact of combined or multiple exposure, the review identifies the most frequent combinations of stressors and modifiers, as well as the extent to which they affect the Risk Characterization Ratio or the Odds Ratio (OR) for mortality/morbidity compared to single stressor exposure. The comprehensiveness of the review is enhanced by the identification of best examples; these are presented in more detail, indicating the health impact of multiple exposure situations and providing detailed data on exposure levels and health effects. Special attention is paid to potential indications of inequalities and socioeconomic and demographic disparities associated with multiple exposures, since SES is known to be related to thermal discomfort, crowding, inadequate hygiene standards, and cheap building and furnishing materials. Synthesis of all this information is quite challenging, due to the need for a multidisciplinary overview of different scientific areas, coupled with a robust and in-depth analysis of exposure and risk characterization for multiple types of stressors.

1.2 Structure of the report

The structure of the report is as follows:

- Chapter 2 shortly provides an overview of the data sources and the methods applied for the systematic review
- Chapter 3 identifies some of the key data on exposure and combined exposure in indoor environments derived from international datasets
- Chapter 4 summarizes the main results of the literature review, broken down into the three settings covered by the report (residential dwellings, schools/kindergartens, and daycare centers)
- Chapter 5 provides a synthesis compiling the key results of the review, listing the most frequent combinations of exposure, discussing their health relevance, and describing social and demographic disparities in exposure
- Chapter 6 presents selected case studies, indicating adequate scientific approaches for the identification of multiple and combine exposure
- Concluding remarks finalize the main report in chapter 7, aiming at the discussion of the report findings in scientific, practical and political contexts
- Finally, chapter 8 provides the reference section listing all literature used in the context of the report (including literature referred to in Annex sections)

The report is enriched by various Annexes, which represent the full material reviewed. The three Annexes focus on

(1) the combination of search terms and respective studies identified during the review;

(2) a more extensive presentation of studies covering combined exposure situations, separated by settings and exposure; and

(3) a discussion of the health relevance of indoor pollutants covered by the studies on combined exposure.

As the studies and results discussed in the main report have been selected from the more extensive Annex material, some material is presented in both the annex and the main report. Furthermore, as several studies cover various settings, exposure factors or health outcomes, in the Annexes a number of studies are presented repeatedly.

1.3 Acknowledgments

2. Methodology

2.1 Compilation of statistical data

A variety of international databases provide information on the quality of built environments, although mostly the archived data refer to private homes. The databases allow looking at the combination of exposure to individual risk factors, and sometimes even provide some health outcome data that could be explored in relation to exposure.

The main data sources used are the WHO LARES survey (Large Analysis and Review of European housing and health Status), the Statistics on Income and Living Conditions (EU-SILC) from Eurostat, and the European Quality of Life Survey (EQLS2012) coordinated by the European Foundation for the Improvement of Living and Working Conditions.

The WHO LARES survey was carried out in 2003 and provides self-reported and objective inspection data on more than 8000 residents and 3300 dwellings in eight European cities (Angers, Bonn, Bratislava, Budapest, Ferreira do Alentejo, Forli, Geneva, and Vilnius). The survey focused on housing and health associations and, therefore, enables a very detailed assessment of both multiple exposure and associated health effects. The database is owned by the WHO Regional Office for Europe, and the results presented have been provided by the WHO European Center for Environment and Health.

EU-SILC is an annual survey on housing and living conditions that is mandatory for all EU members, and is also carried out in some other European countries. It provides nationally representative data on a variety of housing and social conditions, and enables stratification of data by e.g. sex, age, income, and household type. Data can be accessed through an interactive Eurostat web site (Eurostat 2013).

EQLS2012 is a survey carried out every few years and aims at providing data on the quality of life of European residents in relation to work, housing, social, and environmental conditions. The 3rd EQLS was carried out in 2011 and 2012. The database can be requested through the Foundation's web site and data can also be accessed online (Eurofound 2013). The results presented in the report have been provided by the WHO European Center for Environment and Health based on analysis of the full EQLS2012 dataset.

Unfortunately, no similar databases were identified for exposure and conditions of public settings, such as schools, kindergartens and day care centers.

2.2 Systematic Review structure and criteria

PRISMA flow of information was used for carrying out the systematic review. PRISMA focuses on ways in which authors can ensure a transparent and complete reporting of this type of research (Fig. 1). The latter was necessary due to the large amount of literature appearing to be relevant to the key search terms.
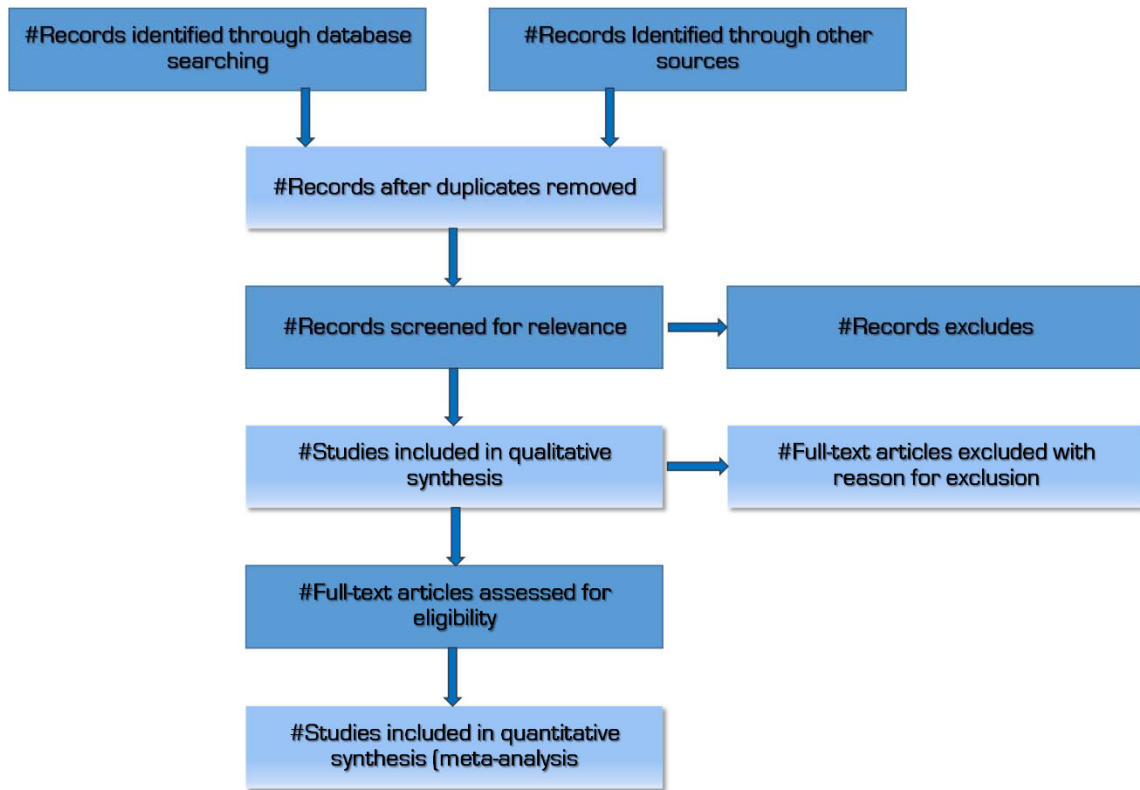
Fig. 1. The PRISMA flow diagram, depicting the flow of information through the different phases of a systematic review (Moher et al., 2009)

The SCOPUS online database was searched for studies related to the assessment of cumulative risks within indoor environments. Publications within the review fulfill specific matching criteria, such as:

- Publication date: only publications after 2005 were included
- Language: only publications in English
- The review was limited to European evidence primarily, even though publications referring to indoor stressors in other WHO regions were considered to provide context to the findings of this study.
- The study should describe exposure conditions where exposure to multiple stressors was observed
- The study should include only residential buildings, day care centers, and school/kindergarten settings

The identification of relevant publications used a systematic approach to search throughout a variety of databases (Scopus, PubMed). Several types of keywords were utilized in varying combinations to cover the wide range of environmental stressors, and exposure modifiers such as 'indoor pollution' needed to be covered as well. Due to this combination of keywords to focus on the indoor settings of interest in combination to the names of stressors of interest, the number of identified studies was reduced. In addition, despite the diversity of the study, only a certain range of studies identified was considered as relevant due to the specific criteria applied. The most frequent reasons for not including studies in the review were: (a) the evidence was based on non-European data; (b) the study referred to occupational or public building settings; (c) the study did not address the resulting exposure to multiple stressors. The given search terms are presented in Annex 1, presenting the results of the extended literature survey undertaken in this frame of this study.

Due to the extensive search terms used, it is unlikely that this review fails to cover the actual existing evidence. Some papers known to the authors and used in this review were actually not identified during the literature search, as they were not primarily published as combined exposure papers. The same accounts for reports by governments, international organizations, or EU funded projects, which provide a significant share of the evidence, but are not accessible through literature search programs. We also hand-searched bibliographies of identified publications for additional references. Moreover, we repeated the search using the name of the chemical air pollutant identified from those papers that were initially chosenas being suitable for inclusion in our review. In order not to lose information due to terminology inconsistencies (authors interchangeably refer to houses, dwellings, homes for the same location), different combinations of search terms were also examined.

The results of the official and grey literature survey were categorized by indoor setting distinguishing between

- Residential dwellings
- Schools and kindergartens (attended by children above 4 years old)
- Day care centers (attended by children below 4 years of age)

In each setting the following combined exposure profiles were assembled for intercomparison:

- Chemical mixtures and classic and emerging indoor pollutants
  These include all chemical pollutants in the indoor environment (in the air, particle and dust phase) comprising carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), particulate matter (PM[1]), ultrafine particles (UFP), volatile organic compounds (VOC), carbonyls, polycyclic aromatic hydrocarbons (PAH), brominated flame retardants (BFR), polybrominated diphenyl ethers (PBDE), polychlorinated biphenyls (PCB), phthalates, insecticides, and other indoor pesticides or biocides.

- Chemical, biological and physical stressors
  This group includes chemical stressors, such as the ones outlined above, combined with biological contaminants (primarily mould and dampness, allergenic fungi, and VOC of biological origin) and physical stressors (thermal discomfort, UV radiation, radon, noise).

- Physical and biological stressors and adverse indoor conditions
  This group comprises physical and biological stressors outlined above with adverse indoor conditions, such as hazardous building materials and furnishings, injury-prone materials and interior architecture, fire hazard, and crowding.

The results of the survey are outlined in the next chapter along with a synthesis and critical evaluation of these results and of the respective drivers.

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[1] PM is broken down into various categories, depending on the size of particles. Particles with aerodynamic diameter of 10 micrometres or less are defined as PM_{10}, while fine particles ($PM_{2.5}$) have an aerodynamic diameter of 2.5 micrometres or less. PM_1 refer to particles with an aerodynamic diameter of below 1 micrometer. Ultrafine particles (UFP) indicate particulate matter of nanoscale size (less than 100 nanometres in diameter).

3. International statistics

Data from EU-SILC for 2011 show that 0.3% (equaling about 1.5 million individuals) of the EU population are considered to live in "deprived" housing, which combines four environmental problems: humidity and dampness, lack of a shower or bath, lack of private toilet, and not enough light. In the Eastern part of the EU, this percentage is as high as 1.3%. A much greater percentage of the population (0.9% for the whole EU (EU-27), and 3.7% for the 12 new Member States that joined the EU since 2004 (NMS-12[2])) lives in housing affected by three of the four mentioned problems.

In 2011, 5.5% of the EU population suffered from severe housing deprivation, defined as an overcrowded dwelling in combination with one or more of the above-mentioned housing deprivation measures. In five EU Member States, more than a tenth of the population faced severe housing deprivation, with the share rising to 17.9% in Latvia, and 25.9% in Romania. Across all EU countries, low income is associated with increased exposure levels to housing deprivation (Fig. 2).
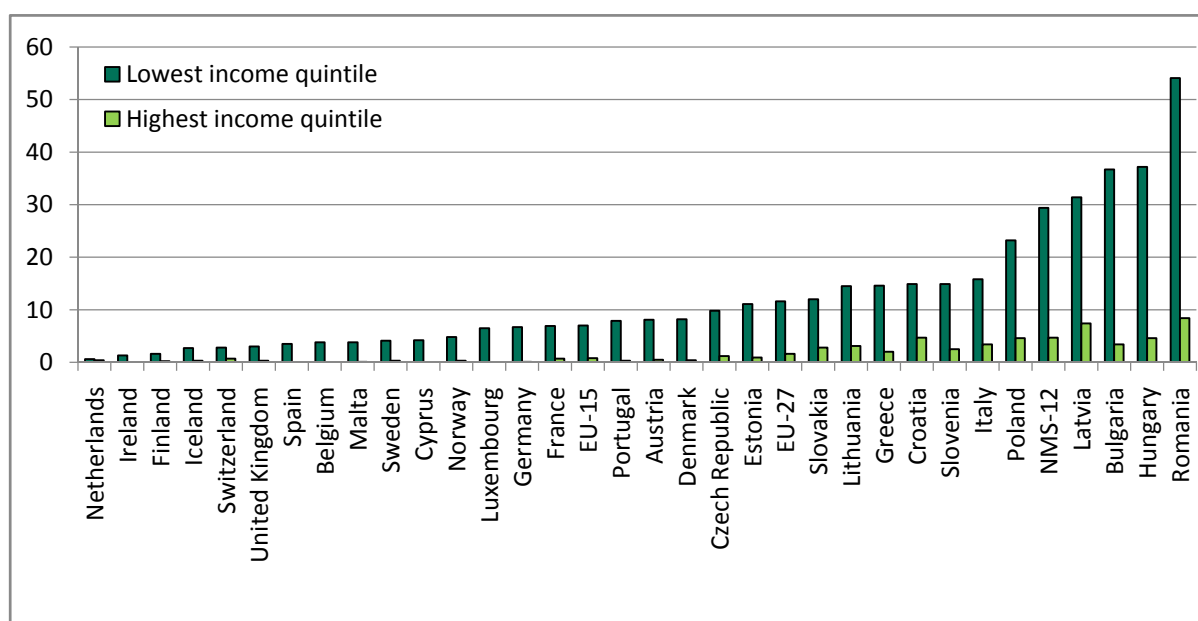
Fig. 2. Severe housing deprivation rate in% by lowest and highest income quintile (2011)

Source: Eurostat, EU-SILC

Similar concerns exist regarding deprivation related to the housing environment – 3.6% of all EU households reported being affected by noise, fear of crime, and outdoor environmental pollution in parallel. However, no major variation exists between the EU-15 (EU members prior to 2004) and the NMS-12 on the environmental dimension. By way of example in Germany 5.4% of the population reports deprivation of their housing environment and in Bulgaria 5.7% of the population reports the same.

The European Quality of Life Survey (EQLS) 2012 covered eight housing problems (noise, air pollution, lack of space, problem to heat dwelling, dampness, problems with drinking-water, lack of toilet, lack of bath or shower). Data analysis shows that 8.8% of the surveyed

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[2] NMS-12 excludes Croatia which joined the EU in 2013

population reported being exposed to at least four of these housing problems. Again, eastern European countries perform much worse (11.9% for the NMS-12 compared to 4.4% for the EU-15; with highest percentages going beyond 18% for Romania and Bulgaria, and beyond 25% for Turkey), and only about 37% of the surveyed population reported having no housing problem at all (44.9% in the EU-15; 28.6% in the NMS-12).

In the EQLS2012, being at risk of poverty more than doubled the risk of being exposed to inadequate housing conditions in comparison to the population without poverty risk (16.3% versus 7.4%). Unsurprisingly, exposure to multiple housing risks is associated with a decreased health status (Fig. 3).
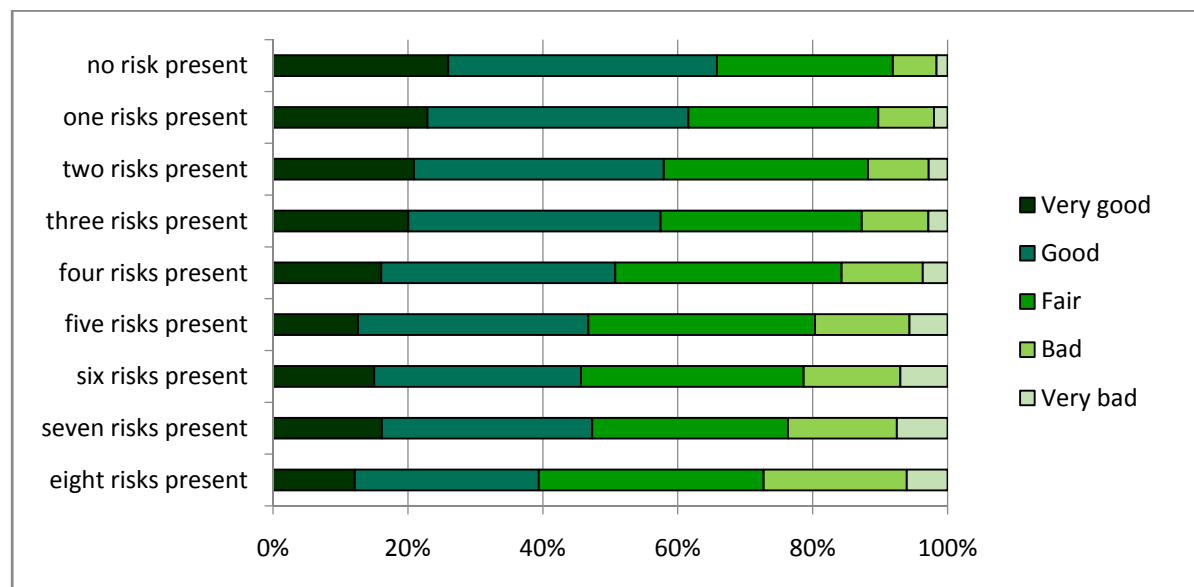
Fig. 3. Self-reported health associated with number of reported housing risks (2011/2012)

Source: Eurofound, EQLS2012

Finally, the WHO LARES survey enables a detailed insight into the prevalence of and health status associated with multiple housing exposure based on data from eight European cities. A multiple exposure score covering 14 risk factors was produced, covering the following dimensions:

- reported thermal problems in summer (often/permanent: 20.6%),
- reported thermal problems in winter (often/permanent: 20.4%),
- missing daylight (24%),
- reported dampness (often/permanent: 16.3%),
- reported mould growth (often/permanent: 11.4%),
- reported indoor air quality (IAQ) problems (dissatisfied/very dissatisfied with IAQ: 10.3%),
- reported presence of mice in dwelling (20.9%),
- crowding (less than 1 room per person: 18.7%),
- reported noise exposure (often/permanent: 20.1%),
- problems with water quality (often/permanent: 10.9%),
- problems with bathroom equipment (dissatisfied/very dissatisfied: 16.8%),
- reported child safety risks in dwelling (based on inspection assessment: 28.7%),
- diminished residential area assessment (bad/very bad area, based on resident perception: 7.3%), and
- lack of safety in neighbourhood when dark (based on resident perception: 18.7).

Analysis of the multiple exposure score indicates that 16.5% of the population are exposed to at least five risk factors in parallel, while 9.8% even report combined exposure to six and more housing-related risk factors. With a rising number of housing risks, the self-reported health status of the residing population decreases significantly (Fig. 4) and the percentage of residents reporting bad or very bad health increased from 5.2% (residents reporting no housing risk) to 12.9% (residents reporting eight or more housing risks). Similar effects of multiple exposure were found for mental health symptoms, and an increased prevalence of certain health conditions such as allergic symptoms, cardiovascular, and respiratory diseases.

Furthermore, the LARES data provides evidence that dwelling deprivation, measured by the multiple exposure score, also seems to affect the risk of injuries. Dwellings identified as having an increased number of environmental and structural hazards were associated with an increased incidence of home injuries in the year prior to the survey. While on average 25.8% of all households reported accident occurring to a household member during the last year, the risk of such accidents was lower when no housing risks were present (18.5%), and much higher when eight or more risks were reported (47.1%).
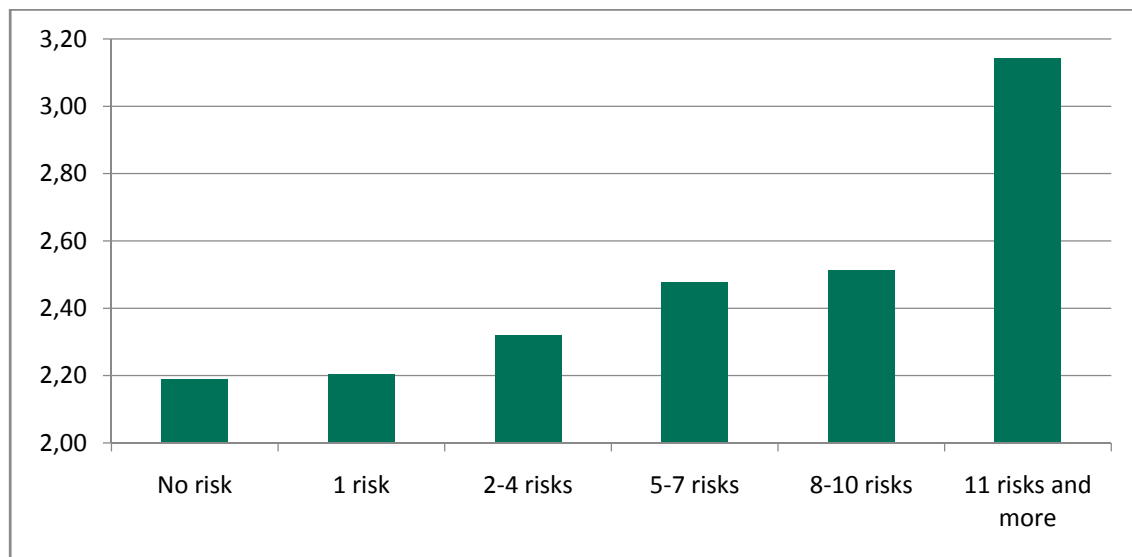
Fig. 4. Mean value of self-reported health associated with number of housing risks (health assessment based on a scale 1 (very good) to 5 (very bad))

Source: WHO LARES database

Similar to the other findings presented above, the LARES survey also indicates that socioeconomic aspects play a major role for the risk of multiple exposure. This is especially valid for income, which might be the strongest socioeconomic determinant for housing quality. Within the LARES data, the mean value for the multiple exposure score – indicating the average number of housing risks – goes down from 3.0 for the lowest income group to 2.0 for the highest income group, showing that on average the poorest households are exposed to three risk factors, while the richest households only report two risk factors (Fig. 5).
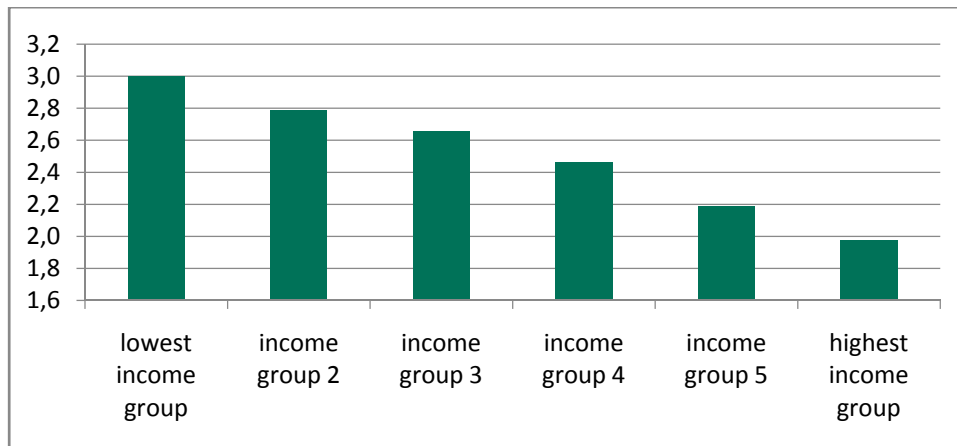
Fig. 5. Mean value of multiple exposure score for income groups

Source: WHO LARES database

In summary, the data from these three international surveys provide convincing evidence that multiple environmental exposure in residential housing, as reported by the residents:

- is widespread throughout Europe, with a considerable proportion of the housing stock being affected by multiple risks,
- especially affects the more vulnerable population groups, and
- is significantly associated with poor health outcomes.

Unfortunately, no databases with similar information were identified for schools, kindergartens or day care centers.

4. Literature review on indoor settings

4.1 Residential buildings

Chemical mixtures/indoor pollutants

Several studies on combined exposure rely on multiple compounds within the same chemical class (e.g. benzene, toluene, ethyl-benzene and xylenes, defined as BTEX) or between chemical classes (e.g. aromatics and carbonyls) without examining biological or physical health stressors. Studies related to combined exposure on multiple compounds within the same chemical class are presented in the Annex section of this report (Annex 2), while the main conclusions derived from the studies including different chemical classes are given below.

With regard to carcinogenic compounds, in a study carried out in Stockholm (Sweden), Yazar et al. (2011) revealed that personal exposure to Class I carcinogenic compounds benzene and 1,3 butadiene was higher than levels associated with traffic, indicating the presence of significant indoor sources contributing to an increased cumulative risk of cancer. These findings are supported by other similar studies; Santamouris et al. (2007) demonstrated that in Athens (Greece), indoor smoking contributes to a significant increase in indoor concentrations of CO, VOC and PM mixtures. Similar results were also disclosed by Saraga et al. (2010), identifying that the presence of SHS is by far the dominant parameter of indoor PM and BTEX concentrations, exceeding the contribution from nearby traffic sources. The deleterious effects of SHS were also highlighted by Castro et al. (2011a) and Slezakova et al. (2009), who found increased content of PAH in both phases (gaseous and particles phase). Based on the measured PAH levels, lung cancer risk for non-smoking occupants living in a house with a smoker was up to 2.5 times higher compared to residents living with non-smokers. The WHO Regional Office for Europe (2011) recently issued a guidance report that describes methods to estimate the disease burden caused by inadequate housing conditions. Among the several risk factors considered, SHS was found to be the most detrimental to human health, associated to a mortality rate of 7.3 per 100,000 (i.e. mortality risk of $7.3 \cdot 10^{-5}$) exposed residents and an overall amount (including all related health endpoints) of 713,000 disability-adjusted life years (DALYs) per year.

Beyond the presence of SHS, several other indoor sources contribute to increased cancer risk. In the review carried out by Belpomme et al. (2007) it was shown that indoor air is a mixture of several carcinogens (SHS, PAH, formaldehyde, benzene, 1,3-butadiene), all of them contributing to a higher cumulative cancer risk, highlighting also the increased relative risk of leukemia and lymphoma caused by the combined presence of indoor VOC and indoor use of insecticides. With similar scope, the comprehensive review by Sarigiannis et al. (2011) covered studies published within the last twenty years (1990-2008), summarizing data on the occurrence of major organic compounds focusing on various indoor environments in Europe. The review revealed significant differences in indoor air quality (IAQ) levels within and among the countries where data were available, also providing risk estimates for the real life mixture of chemicals occurring in European buildings and evaluating cancer and non-cancer risks. Among non-cancer risks, endocrine disruption is a continuously emerging concern. The study of potential endocrine disruptors found indoors carried out by Dirtu et al. (2012) in Iasi (Romania) investigated several organohalogenated contaminants (including pesticides, flame retardants, and PCB) in settled dust. The overall low concentrations found indicate the low usage of goods containing endocrine disruptors in Romanian households.

Additional parameters affecting indoor environmental quality regarding housing include ventilation, type of cooking appliances, proximity to intense traffic (Schembari et al., 2013), ventilation filter efficiency (Wichmann et al., 2010), and presence of open fire for cooking and space heating (Ryhl-Svendsen et al., 2010). Beyond the existence of direct and indirect sources of pollution, indoor air chemistry is also significant for the overall puzzle of combined exposure. In Paris (France), Rancière et al. (2011) confirmed that the presence of ozone and its potential precursors, such as indoor styrene and the frequent use of air fresheners, containing unsaturated volatile organic compounds (e.g. terpenes), results in increased concentration of aldehydes (especially formaldehyde and hexaldehyde). More complex associations occur from the use of cleaning products such as bleach, which effectively inactivates biological allergens, but increases the presence of VOC found in indoor environments (Zock et al., 2009).

Chemical, biological and physical stressors

Studies including chemical, biological, and physical stressors are more comprehensive and provide also some limited findings on risk modification under multiple/combined exposure. Among them, the study by Hulin et al. (2010) is the most compelling, identifying that exposure to biological factors results in neutrophilic airway inflammation, increasing the susceptibility to formaldehyde and toluene exposure for asthma development. Similarly, from the Billionnet et al. (2011) study, a significant positive association was found between asthma and a global VOC score, with an odds ratio (OR) of 1.07 (95% confidence interval (CI) 1.00–1.13), i.e. a risk of disease 1.07 times higher for each one additional VOC with a high exposure level. Haverinen-Shaughnessy et al. (2007) assessed the combined exposure to particles of biological and chemical origin, detecting statistically significant ($p < 0.05$) positive associations between particle mass and blocked nose, total bacteria and both cough and blocked nose, viable fungi and headache, and viable bacteria and eye symptoms. Sahlberg et al. (2013) illustrated that Sick Building Syndrome (SBS) was positively associated to the presence of specific Microbial Volatile Organic Compounds (MVOC) emitted from airborne (mostly) or settled mould, formaldehyde, and plasticizer texanol. These results are in good agreement with the mechanistic hypothesis that exposure to biological factors enhances susceptibility and, thus, adverse health outcomes resulting from indoor formaldehyde exposure (Hulin et al. 2010). LARES Survey reports (WHO Regional Office for Europe, 2007; WHO Regional Office for Europe, 2009a) conclude that insufficient housing conditions are strongly correlated to low SES, which affects most housing risk factors.

The rest of the studies reviewed dealt with monitoring the indoor environment and reporting the presence of multiple chemical compounds and other indoor risk factors. The study by Duboudin (2009) summarizes the correlation between different types of chemical families and other types of indoor risks such as physical (temperature, relative humidity), radiological (gamma radiation and radon) and biological stressors. Mentese et al. (2012) identified bioaerosol levels and species, VOC levels, and fine particulate matter ($PM_{2.5}$) levels in four different environments (house, office, kindergarten, and primary school) along with outdoor sampling. Schlink et al. (2010) found that in many dwellings elevated VOC concentrations were positively correlated to apartments with reported damages due to dampness; the latter is attributed to intensification of VOC emissions from furniture and building materials.

The studies related to physical stressors focus mostly on the adequacy of ventilation for achieving sufficient levels of IAQ, in combination with adequate acoustic performance and minimum energy consumption for achieving thermal comfort (Shahrestani et al., 2013). In the study of Singer et al. (2012), the most notable finding is that for many commercial cooking exhaust devices, achieving capture efficiencies that approach or exceed 75% of indoor air

pollutants requires operating them at settings that produce prohibitive noise levels. Limited studies examine both acoustic and visual comfort in a wider perspective of indoor dwellings and human well-being (Mlecnik et al., 2012; Sarbu and Sebarchievici, 2013). With regard to well-being, Heiselberg and Perino (2010) concluded that short-term window airing is very effective and can provide both acceptable IAQ and thermal comfort conditions in buildings.

Physical and biological stressors and adverse indoor conditions

Prevalence of SBS is found to be enhanced by the combined action of exposure to biological agents and chemicals (Haverinen-Shaughnessy et al., 2007; Sahlberg et al., 2013), especially SHS (Hulin et al., 2012; Jedrychowski et al. 2007; Pirastu et al., 2009; Sahlberg et al., 2009) or additional parameters related to thermal conditions, safety and satisfaction/discomfort (Turunen et al., 2009). In the study conducted by Liebhart et al. (2007), the most significant risk factors (among several others, such as SHS exposure in home, use of gas stoves, owning of pets, or exposure to ambient air pollution) for asthma in adults are predicted to be living in damp (OR 1.53; 95% CI 1.29–1.81) or overcrowded houses (OR 1.35; 95% CI 1.05–1.75). Jackson et al. (2013) have reviewed seven risk factors for severe acute lower respiratory infections (ALRI) in children. Among housing conditions, crowding had an odds ratio of 1.96 (1.53-2.52) and exposure to indoor air pollution provided an OR of 1.57 (1.06-2.31). The Night Noise Guidelines published by the WHO Regional Office for Europe (2009b) report an association between sleep disturbance and accidents found by the LARES survey, with 22% of those reporting an accident also reporting disturbed sleep. Moreover, it is compelling that noise induced sleep disturbance is clearly related to domestic accidents (OR 1.6, 95% CI 1.4-1.9) (WHO Regional Office for Europe, 2007).

4.2 Schools/Kindergartens

Chemical mixtures/indoor pollutants

There are only two studies pertaining to association between multiple chemicals and potential health effects in schools – by Simoni et al. (2010) and Annesi-Maesano et al. (2012). Simoni et al. found that schoolchildren exposed to carbon dioxide (CO_2) levels >1,000 ppm showed a significantly higher risk of dry cough (OR 2.99, 95% CI 1.65-5.44) and rhinitis (OR 2.07, 95% CI 1.14-3.73). By two-level (child, classroom) hierarchical analyses, CO_2 was also significantly associated with dry cough (OR 1.06, 95% CI 1.00-1.13 per 100 ppm increment) and rhinitis (OR 1.06, 95% CI 1.00-1.11). Nasal patency was significantly lower in schoolchildren exposed to PM_{10}>50 μg/m^3 as compared to those exposed to lower levels. Annesi-Maesano et al. revealed a significant positive correlation between $PM_{2.5}$ levels and acrolein and exercise-induced asthma in the same week.

The rest of the studies dealt with assessment of IAQ in school environments. Wichmann et al. (2010) aimed to identify the extent of $PM_{2.5}$, soot, and NO_2 infiltration from the ambient air indoors, concluding that median indoor/outdoor ratios were 0.94, 0.67, and 0.96 for $PM_{2.5}$, soot and NO_2, respectively, influenced by the micro-environment, ventilation type, and air exchange rate. Molnár et al. (2007) found indoor/outdoor ratios for sulphur (S) and lead (Pb) equal to 0.6, suggesting an outdoor $PM_{2.5}$ particle net infiltration of about 0.6 in such buildings (in the lack of indoor sources). Fromme et al. (2006) assessed CO_2, PM, and VOC during a school day in German classrooms. The median values for PM_{10} and $PM_{2.5}$ in classrooms ranged from 16.3 to 313 μg/m^3 and 2.7 to 81 μg/m^3 respectively, with PM concentrations in summer significantly lower than in winter. The work of Sarigiannis et al. (2011) summarized more than two decades of work on VOC and carbonyls. As an example of pollution levels in southern European locations, Greek schools/kindergartens accounted for

an average value of 5.33 μg/m^3 (3.1 μg/m^3 – 7.8 μg/m^3) for benzene and 16.55 μg/m^3 (13.8 μg/m^3 – 20.2 μg/m^3) for formaldehyde. These results are in agreement with the data reported by Missia et al. (2009) who measured an average concentration of 5.5 μg/m^3 for benzene and 12.95 μg/m^3 (4.9 μg/m^3 – 21 μg/m^3) for formaldehyde in three different schools in Greece. For the same chemical compounds, Dutch schools/kindergartens show lower average values for benzene (1.42 μg/m^3, CI 0.8 μg/m^3 – 3.0 μg/m^3) and about similar average values for formaldehyde (13.93 μg/m^3, CI 6.1 μg/m^3 – 22.4 μg/m^3). The work of Stranger et al. (2007) provided more data regarding indoor concentrations of BTEX as well as PM$_{2.5}$ and NO$_2$ in 27 schools in Antwerp (Belgium). Analysis of their data by school location concluded that BTEX concentrations were always higher in suburban than city center schools. Concentrations of formaldehyde were also lower in schools/kindergartens as opposed to homes, however, in this case the difference is lower than for BTEX – an evidence of common sources of emission, such as construction products and furniture, present in both indoor setting types.

Chemical, biological, and physical stressors

Regarding the chemical and biological stressors analysis, Pénard-Morand et al. (2010) found robust associations of lifetime asthma with benzene, sulfur dioxide (SO$_2$), and PM$_{10}$, as well as of sensitization to pollens with PM$_{10}$. The associations of lifetime asthma with benzene (1.3 (1.0–1.9); p=0.04) and PM$_{10}$ (1.4 (1.0–2.0); p=0.05) persisted for the children residing at the same address since birth. Wallner et al. (2012) comprehensively studied air pollution (all chemical classes, biological allergens, and thermal comfort) in schools in Austria and its effect on lung function. There was a negative association between airflow in the lungs of schoolchildren and formaldehyde in the air, and benzylbutylphthalate and the sum of polybrominated diphenylethers in school dust. Moreover, ethylbenzene, m-, p-xylene, and o-xylene showed significant negative correlations with Forced Vital Capacity) and Forced Expiratory Volume in the first second). The latter are key indicators of lung function.

The rest of the studies dealt with monitoring of IAQ. Scheepers et al. (2012) evaluated the performance of portable air treatment units (PATUs) regarding PM$_{10}$, VOC, and biological allergens concentrations, while Mentese et al. (2009) studied indoor air pollutants, bioaerosols (bacteria and airborne fungi), VOC and fine particulate matter (PM$_{2.5}$) for five consecutive days in schools and kibdergartens in Ancara (Turkey). Dorizas et al. (2013) identified the overall concentration ranges of various air pollutant in Athens (Greece) with following results: PM$_{10}$: 14.92-166.18 μg/m^3, PM$_{2.5}$: 3.16-31.27 μg/m^3, PM$_1$: 0.72-9.01 μg/m^3, ultrafine particles (UFP): 4188-63093 pt/cm^3, total airborne fungi: 28-2098 colony-forming units (CFU)/m^3 and CO$_2$: 389-1717 ppm. Pegas et al. (2012b) simultaneously evaluated comfort parameters (temperature, relative humidity, CO$_2$ and CO) and indoor and outdoor concentrations of VOC, NO$_2$, PM$_{10}$ and bioaerosols, concluding that daily indoor PM$_{10}$ levels were always higher than those outdoors, except on weekends. This suggests that physical activity of pupils and and coursework highly contributed to the emission and re-suspension of particles.

Physical and biological stressors and adverse indoor conditions

Reduction of noise exposure is often in contradiction to providing sufficient ventilation in classrooms (Mumovic et al., 2009). In noisy areas, the occupants of the classroom (i.e. pupils and teachers) tend to shut windows especially during quiet activities which increases the likelihood of classrooms experiencing thermal discomfort in hot weather, as well as poor air quality due to the lack of sufficient ventilation (Montazami et al., 2012). The needs for sufficient IAQ, lighting, thermal comfort and acoustic performance are mutually contradictory (Viegas et al., 2009). Assessment of thermal comfort in combination with IAQ is carried out by a combination of perception descriptive measures (by response to questionnaires) and field measurements (De Giuli et al., 2012). Common problems reported are high CO$_2$ concentration

levels, which confirm insufficient air exchange (by opening windows) and occasional insufficient lighting. Pupils complained mostly about thermal conditions in warm seasons, poor IAQ, and noise. Aditionally, crowding is confirmed to be a key determinant of IAQ and thermal comfort. In Portuguese high school buildings poor IAQ and thermal comfort were associated with high density of students in classrooms (Dias et al. 2011). Similarly, it has been recognized that overcrowding of classes might overwhelm the building design specifications for sufficient IAQ and thermal comfort (Stankevica 2011). During summertime, IAQ and thermal comfort require maximum natural ventilation by opening both windows and doors (Conceição et al., 2008). Studies in England have found that classrooms are often inadequately ventilated, resulting in increased risk of negative impacts on the pupils (Mumovic et al., 2009), and the authors concluded that it was possible to achieve natural ventilation designs that also met the criteria for indoor ambient noise levels when external noise levels were not excessive. Finally, Heudorf (2008) provided data on PM_{10} in the indoor air of classrooms before and after intensified cleaning. Although cleaning lowered the levels of indoor particles by 20 $\mu g/m^3$, indoor PM_{10} levels were still dominated by indoor factors, such as occupancy and activity level of the persons in the room.

4.3 Day care centers

Chemical mixtures/indoor pollutants

Wichmann et al. (2010) stated that infiltration factors in day care centers were influenced by the micro-environment, ventilation type, and air exchange rate, concluding that indoor environments occupied by children offer insufficient protection against outdoor pollution from combustion-related particles and gases.

Chemical, biological and physical stressors

Roda et al. (2011) studied IAQ in 28 day care centers in Paris for biological contaminants (dust mite allergens, endotoxins, airborne fungi), chemical pollutants including aldehydes, VOC and NO_2, as well as temperature and relative humidity. For all VOC except benzene, indoor concentrations were higher than the respective outdoor levels — a fact related to the presence of VOC-emitting materials and certain activities (such as painting and the necessary hygienic cleaning schedule). However, due to the better ventilation required by law in day-care centers, these levels were lower as compared to those measured in homes. Aldehyde concentrations in day care centers accounted for lower levels as opposed to those in dwellings. On the other hand, NO_2 levels, although lower than the outdoor concentrations, were higher compared to homes, mainly due to proximity to roads and increased ventilation. Contamination with airborne fungi was greater than in homes, which is explained by the penetration of outdoor contamination through more intense ventilation than in residential places. Increased levels of endotoxins found are explained mostly by high occupancy levels and frequent diaper changes. Mite allergen levels were lower than in dwellings mostly due to cleaning schedules and regular washing. Stankevica (2011) concluded that natural ventilation in crowded indoor settings is not always adequate to assure sufficient indoor quality, thus recommending the installation of a more efficient ventilation system (mechanical).

5. Synthesis

5.1 Most frequent combinations of health stressors encountered

Based on the studies reviewed in this report, there are three approaches that can be distinguished when considering assessment of the built indoor environment quality:

1) **Focus on stressors**: Monitoring is based upon targeting specific compounds, usually from the same chemical family (e.g. aromatic hydrocarbons, such as BTEX or phthalates). Sampling is made by a single type of sampler/collector and analysis is carried out utilizing the same analytical technique (e.g. gas chromatography-mass spectrometry most frequently).

2) **Focus on health effects**: Monitoring is based upon the identification of common health effect of stressors, e.g. allergies due to mould/dampness and formaldehyde exposure. Recently, there is a growing interest in health effects of the indoor environment, resulting in a small yet albeit increasing number of studies characterized by wider inter-institutional cooperation (and consequently available expertise and equipment), covering a variety of pollutants.

3) **Focus on stressors resulting from potential sources of risk**, e.g. for indoor environment in buildings in close proximity to busy streets, the main focus is on traffic-related stressors penetrating the indoor environment, such as NO_2, PM and noise.

The vast majority of the studies identified in this report follow one of these approaches and only rarely do they adapt a more holistic approach aiming at identifying a wider spectrum of stressors or health threats encountered in the built indoor environment. However, the fact that several risk factors are not assessed across different environments in Europe does not mean that they are not existent. Below we discuss combined indoor exposure to (a) chemical mixtures; (b) chemical, biological, and physical stressors; and (c) combined or multiple exposure to a variety of health stressors including biological contamination and physical stressors, in combination with adverse indoor conditions, such as crowding and inadequate hygiene.

Chemical mixtures/indoor pollutants

Considering PM as a complex mixture, 55 studies were recorded, followed by BTEX (51 studies), SHS (50 studies), other VOC (49 studies), carbonyl compounds (48 studies), PAH (42 studies), flame retardants (29 studies), phthalates (28 studies), PCB (27 studies), pesticides (27 studies), and metals (23 studies). The frequency of pollutants encountered in the studies reflects, to some extent, the public and scientific awareness of those pollutants that are highly toxic and carcinogenic (e.g. benzene in the BTEX mixture), abundant in indoor environments (carbonyls), or emerging compounds such as PCB, phthalates, and flame retardants related to the extensive use of plastic consumer products and building materials/electronic equipment in modern dwellings and educational settings.

Beyond measurements of multiple compounds of the same chemical classes, different combinations of stressors are encountered. A detailed description of the combinations of various groups of chemicals as well as biological, physical, and other types of stressors is given in Table 1Table 1, summarizing the combinations covered by the reviewed literature.

Table 1. Number of studies identified with respective combinations of multiple exposure

	PM	O₃	NO₂	CO	PAH	VOC	House-hold chemicals	BFR	Phtha-lates	SHS	Radon	Noise	Mould/ damp-ness	Thermal condi-tions	Crowding	Inadequate hygiene standards	Harmful building equipment/furnishing materials	Safety threats
PM		2	7	5	7	11	1	0	1	4	2	0	5	7	0	0	0	0
O₃	2		3	1	0	3	0	0	0	1	0	0	1	1	0	0	0	0
NO₂	7	3		2	1	7	0	0	0	2	0	0	2	3	0	0	0	0
CO	5	1	2		3	7	1	0	1	3	1	0	2	2	0	0	0	0
PAH	7	0	1	3		2	2	0	1	2	2	0	1	0	0	0	0	0
VOC	11	3	7	7	2		2	0	1	4	2	0	9	8	1	1	1	0
Household chemicals	1	0	0	1	2	2		2	1	3	0	1	3	1	1	1	1	0
BFR	0	0	0	0	0	0	2		0	0	0	0	0	1	0	0	0	0
Phthalates	1	0	0	1	1	1	1	0		0	0	0	0	0	0	0	2	0
SHS	4	1	2	3	2	4	3	0	0		0	1	5	3	2	2	1	0
Radon	2	0	0	1	2	2	0	0	0	0		0	2	2	0	0	0	0
Noise	0	0	0	0	0	0	1	0	0	1	0		1	3	2	1	1	0
Mould/dampness	5	1	2	2	1	9	3	0	0	5	2	1		13	3	7	14	0
Thermal conditions	7	1	3	2	0	8	1	1	0	3	2	3	13		1	1	2	0
Crowding	0	0	0	0	0	1	1	0	0	2	0	2	3	1		1	1	0
Inadequate hygiene standards	0	0	0	0	0	1	1	0	0	2	0	1	7	1	1		1	1
Harmful building equipment/furnishing materials	0	0	0	0	0	1	1	0	2	1	0	1	14	2	1	1		0
Safety threats	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	

Among the most frequent combinations encountered in several studies are those for PM (which is a stand-alone chemical mixture) and the "expanded" VOC[3] (including aromatic and carbonyl compounds): in total eleven studies were identified. These studies mainly aim at assessing the effects of multiple stressors regarding common adverse respiratory outcomes, such as asthma, rhinitis and eczema (Annesi-Maesano et al., 2012; Billionnet et al., 2011; Hulin et al., 2010) or lung function (Wallner et al., 2012).

A combination of stressors found frequently includes PM and PAH (7 studies); this is expected since PAH are for the most adsorbed on particles and PM sampling is a requirement prior to PAH analysis. However, there are also a few cases of PAH measurements in the gas phase (Castro et al., 2011b) or adsorbed in other media like settled dust (Mannino and Orecchio, 2008).

Another frequent combination is the assessment of non-carbonyl VOC and carbonyl compounds, covered in 20 studies, as well as the evaluation of the carcinogenic compounds— benzene and formaldehyde within BTEX — and a group of carbonyl compounds, respectively (14 studies). Phthalates are rarely measured in combination to other chemical classes since it requires an analysis of settled dust samples (similarly to PCB), therefore, only three studies have been found with combined exposure measurement of phthalates and other indoor chemicals.

Chemical, biological and physical stressors

The studies of Annesi-Maesano et al. (2012), Hulin et al. (2010) and Billionet et al. (2011) are among the most comprehensive ones, since they provide quantitative associations (OR) of IAQ with respiratory diseases in a large number of residences and schools. In addition, these studies cover a large number of other stressors beyond PM and the "expanded" VOC group, including biological contamination and inorganic pollutants, such as CO and NO_2. Among the reviewed studies, the most comprehensive, in terms of the pollutants considered, is the one by Billionet et al. (2011). In this study, 30 physical, chemical and biological pollutants were measured with a specific sampling strategy for each pollutant (e.g. equipment, protocols for fitting, sample collection and analysis, room used). These pollutants comprised twenty VOC, including four aldehydes, twelve hydrocarbons, and four glycolethers, four common allergens (dust mite allergens (Derp1 and Derf1), and dog and cat allergens (Canf1 and Feld1)), CO, temperature, relative humidity, CO_2, PM, and radon. In terms of pollutants assessed, the study of Wallner et al. (2012) included all the pollutants above, plus chemicals found potentially indoors (including PAH, BFR, phthalates, pesticides and household chemicals). This is the most comprehensive study surveyed in this review in terms of number of health stressors assessed. A broad spectrum of pollutants was also examined in the study carried out by Stranger et al. (2007), covering PM_1, $PM_{2.5}$ and PM_{10} mass concentrations and elemental carbon estimates like black smoke, as well as gaseous NO_2, SO_2, O_3 and BTEX concentrations.

Very interesting studies are those combining measurements of PM and mould/dampness (5 studies). PM measurements were also associated with thermal comfort (7 studies), mostly carried out in the frame of studies evaluating buildings' energy efficiency/insulation rather than for exposure/risk assessment purposes. However, there is an unexpected lack of studies associating combined measurements of noise and PM, considering that both factors are significantly influenced by the proximity of the indoor setting to traffic; there is only one modelling study related to a composite risk index for houses in the frame of life-cycle analysis study of a dwelling in the Netherlands (Meijer et al., 2006).

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[3] Benzene, toluene, ethylbenzene, xylenes, styrene, formaldehyde, acetaldehyde, acrolein, hexanal, pentanal, benzanaldehyde, acetone, propanal

Physical and biological stressors and adverse indoor conditions

Beyond chemical stressors, noise assessment is associated with crowding (2 studies); but the most frequent combination of noise to chemical stressors is related to CO_2, which is a measure of good ventilation and reversely correlated to building insulation and low noise levels. However, noise is mentioned mostly as annoyance rather than a measurement of actual levels of indoor noise.

Regarding the variability between locations, significant differences are related to assessment of SHS (not encountered in schools/kindergarten and day care centers), PCB, phthalates, and flame retardants. The latter are usually found at homes, while in the respective public building assessments the findings refer mostly to PM, VOC, NO_X, and allergens.

5.2 Impact of combined and multiple exposure on risk ratios for reported outcomes

Overall, the impact of the identified combined exposure to health stressors on risk ratios for health outcomesranges from moderate to significant. This evaluation is not exclusively based on the simple additivity of effects (i.e. situations where the health effect of the combined exposure to several stressors can be estimated as the sum of the effects that each individual stressor would have had separately), which is the basic hypothesis for assessing the health risk of exposure to multiple stressors. There is enough evidence of widespread combined non-occupational exposure to a multitude of stressors in the indoor environment, and enough evidence that several health stressors (chemical, physical and biological) may, when combined, indeed result in beyond-than-additive health effects, altering the risk ratios of the reported health outcomes. Still, more studies are needed to derive robust conclusions on the non-additive effect of combined and multiple indoor exposure on public health. Currently, among the many studies addressing the health effects associated with exposure to environmental stressors, only very few studies provide quantitative estimates of the combined effect of exposure to multiple stressors on health outcomes. In the section to follow, we report the most interesting studies with relevance to indoor environment, and in particular, stressors encountered in dwellings, schools, kindergartens and day care facilities.

A clear example of risk modification is presented for a frequent combination of biological and chemical health stressors, namely mould, toluene, and formaldehyde. A study done by Hulin et al. (2010) in France focused on the comparison between urban and rural houses in relation to childhood asthma development. Significant differences were found in the associations according to location; in rural homes the ORs of asthma were significantly increased for elevated exposure to formaldehyde and toluene (OR 10.7, 95% CI 1.69–67.61 and 3.8, 95% CI 1.24-11.77 respectively), while in urban homes, these associations were not significant. The relationships observed at low doses of formaldehyde were attributed to the particular susceptibility of children born and having lived on a farm. However, several studies have actually revealed lower prevalence of allergies in farmers' children, with inconclusive results for asthma (Remes et al., 2005). Potential protective effects of farming have been attributed to early microbial exposure to contaminants, such as endotoxins or fungi, which are widespread in rural areas (Schram-Bijkerk et al., 2005). Conversely, it has been suggested that such exposure could undermine airways by inducing a permanent status of neutrophilic airway inflammation through a mechanism other than non-IgE–mediated[4] pathways and, thus, lead to reversible airway obstruction (Douwes et al., 2002a; Douwes et al., 2002b). Such exposure could generate a higher susceptibility of rural populations to develop non-atopic asthma, because of pre-existing inflammation and, therefore, formaldehyde along with other pollutants could act on the inflamed airways even at low doses. The Hulin et al. study showed that levels of low environmental exposure to ubiquitous chemicals such as formaldehyde and toluene are potentially

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[4] IgE: immunoglobulin E

harmful to susceptible populations if combined with exposure to biological allergens. In this case, even concentration levels below the proposed exposure limits of 30 and 300 µg/m^3 for formaldehyde and toluene, respectively, increase the actual risk of asthma development when combined with continued exposure to biological allergens through the mechanism described above.

Jaakkola et al. (2006) conducted a study addressing the impact of combined and multiple exposure on risk ratios in a population-based incident case-control study. The aim of the study was to assess the relations between different types of interior surface materials and recent renovations at home and at work with the risk of asthma in adults. The authors systematically recruited all new cases of asthma during a 2.5 – year study period (1997–2000) and randomly selected controls from a source population consisting of adults 21–63 years of age living in south Finland. A total of 362 cases (response rate: 90%) participated through the health-care system and 159 cases through the National Social Insurance Institution (response rate: 78%), totalling 521 cases. A questionnaire on the type of interior surface materials at home and at work revealed information on exposure to emissions from these materials. Exposure to dampness and mould was assessed by a questionnaire section on water damages, stains, and other marks of structural dampness, visible mould, and mould odour. Exposure to pets was confirmed by questions on the presence of cat(s), dog(s), bird(s), rodent(s), or other furry animals at home during the past 12 months. Lung function measurements were carried out through spirometry and bronchodilation tests. Furthermore, all patients performed peak expiratory flow follow-up with measurements twice a day for at least 2 weeks. Analysis of data through logistic regression analysis adjusting for confounding factors revealed that the risk of asthma was related to the presence of plastic wall materials (adjusted OR 2.43, 95% CI 1.03, 5.75) and wall-to-wall carpet at work (adjusted OR 1.73, 95% CI 0.74, 4.09); the effect of the latter was particularly pronounced in the presence of mould problems (adjusted OR 4.64, 95% CI 1.11, 19.4). The authors discriminated the effect due to the co-exposure of mould and chemicals emitted from wall-to-wall carpet showing that the adjusted odds ratio of asthma varied from OR 0.77 (95% CI 0.46 – 1.30) for wall-to-wall carpet and no mould to OR 1.51 (95% CI 0.30 – 7.64) for wall-to-wall and mould in homes. In the work environment the combined effect was enhanced with an OR ranging from OR 1.43 (95% CI 0.69 – 2.69) for wall-to-wall carpet and no mould to OR 4.64 (95% CI 1.11 – 19.4) for wall-to-wall and mould. Comparing these results with findings of the European Community Respiratory Health Survey, which reported that mould exposure was associated with asthma symptoms and bronchial responsiveness with an OR ranging from 1.14 to 1.44 (Zock et al., 2002), it can be concluded that co-exposure to chemicals from carpeting and mould produces adverse health effects beyond additivity (compounded effects).

Another relevant study was conducted by Sarigiannis et al. (2012) regarding co-exposure to BTEX across Europe based on an EU-wide review of actual population exposure to these chemicals indoors. The authors investigated the health effect (i.e. leukemia and neurotoxicity) associated with exposure to benzene alone and in combination with other VOC. The study followed a mechanistic approach entailing the application of multicompartmental physiologically-based pharmacokinetic/pharmacodynamic model which takes into account the interaction (i.e. competitive inhibition of metabolism between the four chemicals that compete as substrates for the same isoenzyme (P450 2E1)) among the mixture constituents to estimate the biologically effective dose (BED) in the target tissue (bone marrow) of the benzene metabolites (benzene oxide, phenol, and hydroquinone), the latterbeing associated with leukemia. Model results were validated against human biomonitoring data of occupants exposed to benzene. Finally, the model was linked to a pathology model to associate the probability of leukemia risk to the total concentration of benzene metabolites in urine. Results showed that at the levels of environmental concentrations found in indoor locations, no significant mixture interaction is manifested at the metabolic level; thus, co-exposure to BTEX does not pose any reason for additional concern if these contaminats were to be assessed as individual substances. However, the authors pointed out that the interaction effect due to concurrent exposure to a chemical mixture becomes evident when the exposure levels are higher with respect to typical environmental exposures. This is the case for occupational exposure

characterized by exposure levels of the same order of the threshold limit value for all the four substances composing the mixture. Under such an exposure scenario, benzene concentration in the bone marrow is higher under combined exposure to BTEX as opposed to exposure to benzene alone at the same concentration level. The increment can be estimated between 25% and 30% leading to an increased risk of neurotoxicity and analogously reduced risk of leukemia for healthy individuals after lifelong exposure.

A further study addressing the impact of combined and multiple exposure on risk ratios is the work of Nickmilder et al. (2007) who investigated to what extent regular house cleaning with bleach can influence the risks of respiratory and allergic diseases in children. The study team enrolled 234 children from a population of 341 schoolchildren recruited in Brussels from the fifth and sixth grades of 10 primary schools. Children underwent a detailed questionnaire including 38 questions inquiring among others items about family history of allergic diseases (asthma, hay fever or eczema), recurrent infectious diseases (doctor diagnosed bronchitis, otitis or pneumonia), asthma and allergic diseases (doctor-diagnosed asthma, eczema or hay fever) and respiratory symptoms, as well as questions about lifestyle or environmental factors likely to be involved in the development of respiratory or allergic diseases. They further underwent an exercise-induced bronchoconstriction test and measurements of exhaled nitric oxide (NO) and of serum total and aeroallergen-specific IgE, Clara cell protein, and surfactant-associated protein D. Results revealed that children living in a house regularly cleaned with bleach and consequently exposed to volatile chlorination products were less likely to have asthma (OR 0.10; CI 0.02–0.51), eczema (OR 0.22; CI 0.06–0.79) and of being sensitized to indoor aeroallergens (OR 0.53; CI 0.27–1.02), especially house dust mite (OR 0.43; CI 0.19–0.99). These protective effects were independent of gender, ethnicity, previous respiratory infections, total serum IgE level, and family history of allergic diseases. Moreover, it is interesting that the above protective effects were nullified by parental smoking, which also interacted with the use of bleach to increase the risk of recurrent bronchitis (OR 2.03; CI 1.12–3.66). The study concluded that cleaning with chlorine bleach appears to protect children from the risks of asthma and sensitization to indoor allergens, however, during co-exposure to SHS the risk of recurrent bronchitis increases. This study demonstrated that combined exposure to SHS and chlorine bleach has a potentially negative effect on respiratory health of children.

5.3 Socioeconomic and demographic disparities as modifiers of exposure and health impact

A recent report from the WHO Regional Office for Europe (2012) provides a comprehensive assessment of environmental health inequalities in the WHO European Region. As such, it represents a comprehensive and detailed review on the existence of socioeconomic and demographic inequalities in exposure to environmental hazards across Europe, with most data available for the EU. The report systematically covers the interaction between environmental health and SES through the definition of a set of 14 environmental health inequality indicators. Two aspects of housing inequality are distinguished from a public health perspective: inequalities related to the basic needs for water and equipment for drinking, cooking, and hygiene, and inequalities related to overcrowding, dampness, and the capacity to keep the home warm or cool. The main health effects associated with water and sanitation indicators are infectious diseases, while those associated with the latter indicators are allergic and respiratory or cardiovascular diseases. Further data analysis reflects the distinction between these two different aspects, showing that the former is of particular concern in the 12 new EU Member States (NMS-12)[5], whereas the latter affects both the NMS-12 and the EU-15. The analysis also clearly demonstrated that a high proportion of the population living in the NMS-12 countries has no flush toilet and no bath or shower in the dwelling. The report

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[5] EU member states that joined between 2004 and 2007, not including Croatia which joined in 2013.

concluded that absence of sanitation equipment inside the home may have considerable health consequences, and that housing policies should ensure that all new residences in public buildings or private houses offer basic commodities. Accessibility and affordability of drinking-water has also been shown to be a serious issue in many countries of the Eastern part of the WHO European Region and especially central Asian countries– particularly, but not solely, in rural areas. Moreover, the analysis revealed that although the prevalence of inadequate water supply had a decreasing trend for all countries since 1995, it has remained high for countries belonging to the former Soviet Union (except for the Baltic states).

The data provide strong evidence that the non-sanitary housing inequalities – overcrowding, dampness, and thermal comfort related to cool and warm homes – exist in almost every country. Once again, low-income populations, and especially low-income single-parent households, are most affected across all indicators. Prevalence of self-reported noise annoyance varies considerably between countries. Irrespective of social differences, a relevant proportion of the population in many countries is affected by noise from neighbours or from the street. In EU-15 and western European countries on comparable developmental level (such as Norway and Switzerland), but not in the Eastern EU countries (NMS-12), prevalence of complaints about noise from neighbours or from the street is higher among individuals with low income. Social inequalities in second-hand smoke (SHS) exposure at home exist with higher exposure among socially disadvantaged groups, characterized by low self-assessed social position, difficulty paying bills most of the time, and unemployment.

A review by Le Cann et al. (2011) focused on children as one of the most vulnerable population groups. The work confirmed that in recent years, it has become apparent that an increasing number of children are socially disadvantaged not only in poor societies, but also in rich countries. This observation is very important as poverty and deprivation in early childhood influence both health and development to various degrees and can have serious lifelong health consequences (Hornberg and Pauli. 2007). There is clear evidence of social health inequalities in most industrialized countries (Kunst, 2007). In general, socioeconomically disadvantaged people are more strongly affected by health problems (Cesaroni et al., 2003; Dalstra et al., 2005; Ellison-Loschmann et al., 2007; Kunst, 2007) as opposed to more affluent people. This is also evident in children. For numerous years, several determinants have been suggested to explain social health inequalities (Goldberg et al., 2003). Individual risk factors have been well documented, and are, generally, more prevalent among the most disadvantaged populations. Recently, it has been suggested that environmental nuisances could also contribute to social health inequalities (O'Neill et al., 2007; Siegrist and Marmot, 2004). Assessing the possibility of environmental exposure explaining social health inequalities is currently a major public health research issue. According to the literature investigating this field, there are two major mechanisms acting independently or in synergy, by which environmental exposures can contribute to social health inequalities. Among the general population, disadvantaged groups are recognized as being more often exposed to sources of pollution (exposure differential) and/or more susceptible to the resulting health effects (susceptibility differential). It has been demonstrated that socioeconomic factors may have an impact on children's environmental health through these two mechanisms (Kohlhuber et al., 2006a). A recent review carried out by the German Federal Environment Agency (Umweltbundesamt, 2009) revealed contrasting findings regarding environmental inequalities related to chemical agents. On the one hand, households of low social status appeared to be more exposed to several indoor environmental nuisances, as children' bedrooms showed a higher benzene level and children also had higher lead concentration in blood. On the other hand, some types of exposures were found more frequently in well-off households, such as PCB-levels in children's blood, terpene concentrations in indoor air, and DDT levels in house dust samples. The same mixed findings were obtained from the German national children and environment study. Recently, using dust lead data from the US National Health and Nutrition Examination Survey, Dixon et al. (2009) demonstrated that the race/ethnicity and date of construction of housing, currently used as indicators of SES, were associated with the children's dust

lead levels. Social inequalities were repeatedly reported for biological indoor pollutants such as allergens and endotoxins. In Germany, Chen et al. (2007) compared the amount of indoor bio-contaminants for mothers and children stratified by socioeconomic group: whereas exposure of children to the cat allergen Fel d 1 was higher in families of low SES, exposure to the dust mite allergen Der f 1 seemed to be more common in families with a high SES. In 2008, Wang et al. (2008) explored the relationship between biological indoor pollutants and health among people living in low-income housing (2/3 of them being children). This study revealed that households living in dwellings infested by mice were nearly twice as likely to be diagnosed with asthma as compared to those not exposed. The exposure differential alone could explain these results as the whole group had a low income and therefore no other SES risk modifiers were identifiable.

Given that socially disadvantaged families tend to live closer to busy roads, noise annoyance due to traffic is often higher in people with a lower SES (WHO Regional Office for Europe 2010b, 2012). From the German Environmental Survey 2003/06 (GerES IV) for children, Babisch et al. (2009) demonstrated that socially disadvantaged children were often more irritated by road traffic noise than children of higher SES. A recent study on children living in Munich showed a correlation between relative poverty and exposure to high traffic noise (WHO Regional Office for Europe, 2010b). Morover, high annoyance to traffic and neighborhood noise was associated with a lower equivalised disposable income and poor housing conditions revealed by the German Health Interview and Examination Survey for Adults (Laussmann et al., 2013).

Bolte and Fromme (2009) analysed the impact of different socioeconomic indicators on the prevalence of child SHS exposure in several indoor environments based on the home smoking policy of the family. The study assessed data on 12,422 pre-schoolchildren (48% female) from two cross-sectional surveys conducted during 2004-06 in Germany. Exposure assessment was based on parental reporting. Low parental education, unemployment, low household equivalent income, non-German nationality, single-parent family, and family size were independently associated with the exposure of children to SHS at home. The authors stated that the strongest associations were observed for low parental education at home: adjusted OR 3.94; 95% CI 3.46-4.49. Indicators of material living conditions (relative poverty: OR 0.48; CI 0.39-0.57, parental unemployment: OR 0.55; CI 0.46-0.65), as well as single-parent family, non-German nationality and family size, but not parental education, were independently associated with SHS exposure at hospitality venues. Smoking households with low parental education, unemployment, poverty, single-parent family, and non-German nationality were less likely to have the rule of exclusively smoking on the balcony or terrace. Low parental education and unemployment were negatively associated with no smoking in presence of the child in households with smoking inside the flat. A similar study has been conducted by Pisinger et al. (2012) who hypothesised that there has been a growth in social inequality in children's exposure to SHS at home over time. The purpose of this study was to investigate temporal change in smoking in homes including children, focusing on the socioeconomic differences. Data came from a repeated cross-sectional survey, Health Profiles of the Capital Region of Denmark conducted in 2007 and 2010, in 29 municipalities enrolling persons aged 25 to 64, living with children 15 years of age; N=9289 in 2007 and 12,696 in 2010. Results showed that there were significant large socioeconomic differences in both 2007 and 2010. In 2010, it was more than 11 times more likely for a child to be exposed to SHS at home if the parent had very low education than if they were highly educated (p<0.001). Smoking in a home with children present decreased from 16.2% in 2007 to 10.9% in 2010. The odds of a temporal decrease in domestic smoking did not differ significantly across parent education levels (p=0.40).

In another study De Meer et al. (2010) investigated the relationships between parental education and respiratory symptoms in their children, distinguishing atopic and non-atopic symptoms. A cross-sectional survey among 3262 elementary schoolchildren (age 8-13) was performed; data on parental education were obtained for 3213 children. Parents completed a questionnaire on their child's allergic and respiratory symptoms, and potential explanatory variables including family history,

indoor environment, and the child's medical history. Subsets of children were tested for atopy (n = 1983), lung function (n = 2325), and airway hyperresponsiveness (n = 880). Results showed that a high parental education was associated with an increased risk of atopic sensitization to indoor allergens (OR 1.31, 95% CI 1.02-1.69). In contrast, a high parental education protected children from wheeze (OR 0.77, 95% CI 0.61-0.97). This only applied to non-atopic wheeze (OR 0.65, 95% CI 0.43-0.99) and not to atopic wheeze (OR 0.89, 95% CI 0.60-1.31). The protection from non-atopic wheeze in children of highly educated parents declined after adjustment for household smoking and breastfeeding (OR 0.96, 95% CI 0.58-1.57). Similar results were observed for non-atopic and atopic rhinitis. The authors concluded that children from highly educated parents are protected from non-atopic respiratory symptoms, which is largely explained by a lower rate of household smoking and a higher rate of breastfeeding.

There is a complex link between noise exposure and household socioeconomic characteristics that appears to differ for indoor and outdoor equivalent continuous sound levels. Indoor noise levels were not found to be associated with any measured socioeconomic factors, and although a lack of statistical power could not be formally excluded, this result could reveal a real difference in the relationships between the family SES and both outdoor and indoor noise exposures (Pujol et al., 2012). These findings could be explained by a greater influence of indoor ''sources'' on indoor noise levels and the dissociation between the outdoor environment and the indoor noise levels. The former point could be attributed to: (a) a high percentage of dwellings having sound noise proofing, including doubleglazed windows; (b) a low percentage of dwellings exposed to high outdoor noise levels; and (c) public policies regarding the thermal and acoustic insulation of dwellings that are applied to both social and private housing. Indoor factors that influence indoor noise levels should be considered as indoor acoustic sources including the total number of inhabitants, the number of children, the number of children sharing the studied bedrooms, and the presence of ''noisy'' equipment. Finally, the difference in the sound level of the noisiest room between collective buildings and detached houses could be explained by a differential occupancy of the dwelling by the inhabitants; children in collective buildings could spend more time in their bedrooms than children living in detached houses (Pujol et al., 2012). Similar results were obtained from the German Socioeconomic Panel longitudinal survey of the German population (Kohlhuber et al., 2006b): perceived exposure to noise was elevated in higher age groups, and East Germans had 44% higher odds to be highly exposed after adjustment for covariates, while no significant associations were observed in the full model with sex and type of family. Within the classical socioeconomic factors (income, education, and occupation) only the equivalent household income showed significant associations with perceived noise exposure.

Similar data exist for air quality perception (Kohlhuber et al., 2006b). Among the sociodemographic variables, female sex, non-German nationality, and living in East Germany were risk factors for perceived high exposure to air pollution both before and after adjustment. Similar to noise, income was significantly associated with perceived high exposure to air pollution, but not educational degree or occupational status. Again, the most significant associations were observed for housing conditions. Living in an industrial area increased the odds of being highly exposed to air pollution by a factor of 2.37. As in the model for perceived noise exposure, crowding was not related to perceived air pollution exposure. From the study, it was also highlighted that ethnic minorities (characterized by lower income) experience a higher risk of being exposed to both indoor air pollution and noise, since people with low income suffered more often from adverse housing conditions, such as air pollution in the neighborhood, dampness, molds, and higher concentrations of indoor pollutants. These population groups also lived more often near main roads with high volumes of traffic, in big apartment buildings, and in houses that need renovation (Kohlhuber et al., 2006b).

6. Best examples – case studies

As scientific knowledge on the health effects of the various agents encountered in indoor settings has evolved, several recent studies focused on the interactions between agents leading to health disorders. Some interesting examples found in recent literature are described below.

Indoor air may contain biologic air pollutants, such as allergens and microorganisms, and chemical pollutants, including nitrogen oxides and VOC. Of the indoor air chemical pollutants, formaldehyde has been identified as the most ubiquitous. Indoor concentrations range from 1 to several dozen $\mu g/m^3$ depending strongly on the materials and furnishings present. Besides its well established irritant effects on the upper respiratory tract and its tumour promotion features, specific IgE sensitization to formaldehyde has been suggested. Another mechanism proposed to explain the health effects of formaldehyde may be an increased risk of allergic diseases. In children, exposure exceeding 50 $\mu g/m^3$ may increase the risk of allergic sensitivity to common aeroallergens. Mite allergen is the most frequent stressor linked to allergic asthma, and group I mite allergen is identified very frequently in the dwellings of mite-allergic patients. Concomitant exposure to house dust mites and formaldehyde in indoor air is undoubtedly common in many indoor settings.

In the work of Casset et al. (2006) nineteen asthmatic subjects (12 women and 7 men were recruited; ages ranged from 19 to 35 years) were enrolled to evaluate the influence of pre-exposure to low-dose formaldehyde (100 $\mu g/m^3$ during 30 minutes according to the WHO-recommended maximum value for indoor environments) on bronchial response to *Dermatophagoides pteronyssinus*. Patients sensitive to seasonal allergens (pollens) were studied outside the relevant pollen season, and those sensitized to cat or dog allergens were included only if they had no pets at home. None of the patients was exposed to formaldehyde from an occupational environment. Each subject underwent a mite allergen bronchial challenge test immediately after a standardized exposure in a chamber to formaldehyde or air (random order). Induced sputum was collected 24 h before and after the patients were exposed to mites. Exposure took place in a chamber under standardized conditions for 30 minutes with a formaldehyde concentration just below 100 $\mu g/m^3$. Pulmonary function tests were run before and after exposure to formaldehyde or air and followed each house dust mite – bronchial challenge test every hour for 6 hours under medical supervision.

Results revealed that formaldehyde exposure for 30 minutes did not cause any changes in lung function and did not induce symptoms. It did, however, significantly enhance immediate and late airway responses to inhaled mite allergen in subjects with mild asthma, suggesting that exposure to low levels of formaldehyde significantly enhanced bronchial responsiveness to mite allergen in mite sensitized subjects with asthma.

A second example of combined exposure regards interactions among chemical agents. There is an increasing amount of information on the health effects of many chemical agents, as reviewed above, especially regarding respiratory symptoms. In his review in 2007, Mendell (2007) had already found that most studies focus on emission-related activities or on the influence of materials on respiratory health, such as painting, cleaning, or presence of plastic materials or particleboard. Recently, nonetheless, a few studies focused on the synergy between known chemical agents.

Among these studies, the work of Nickmilder et al. (2007) aimed to study to what extent regular house cleaning with bleach can influence the risks of respiratory and allergic diseases in children. Chlorine bleach or sodium hypochlorite is the most commonly used disinfecting and cleaning agent in the developed world as it can inactivate common indoor allergens. It is currently used for a variety of applications such as water and food disinfection and cleaning of surfaces in public and private buildings. Advantages of bleach include low cost, easy use, residual protection, deodorizing, and a strong germicide activity against a wide spectrum of microorganisms due to its strong oxidative capacity. Recently, chlorine bleach has also been found to be effective in the inactivation of cat

(Fed1) and house dust mite (Der p1) allergens, suggesting that it might perhaps offer some protection against allergic diseases. However, when mixed with other cleaning agents or when reacting with organic matter or some metals, chlorine bleach can release chlorine or trichloramine, two gases which are strong irritants to the eyes and the respiratory tract.

The study team enrolled 341 children from a population of schoolchildren recruited in Brussels from the fifth and sixth grades of 10 primary schools. Of the 341 children initially enrolled in the study, 107 were excluded because they had a backyard swimming pool, had swum in early ages, or were members of a swimming club. As revealed by recent studies (Bernard et al., 2006; Bernard and Nickmilder, 2006) exposure to volatile chlorination products, when regularly attending swimming pools during early life or as part of a sport activity, are risk factors of childhood asthma likely to confound or to mask the possible effects of bleach use at home.

Children examination included a detailed questionnaire including 38 questions inquiring among others items about family history of allergic diseases (asthma, hay fever, or eczema), recurrent infectious diseases (doctor diagnosed bronchitis, otitis, or pneumonia ever), asthma and allergic diseases (doctor-diagnosed asthma, eczema, or hay fever ever), respiratory symptoms. There were also several questions about lifestyle or environmental factors likely to be involved in the development of respiratory or allergic diseases such as number of siblings, housing density (persons/room), sporting activity, living with pets at home (since birth or from <2 years), exposure to SHS, home cleaning with chlorine bleach (at least once per week), house with double-glazed windows, mould on child's bedroom walls, and living in a rural or urban area. In addition they underwent an exercise-induced bronchoconstriction test and the measurement of exhaled NO and of serum total and aeroallergen-specific IgE, Clara cell protein, and surfactant-associated protein D.

Results showed that children living in a house regularly cleaned with chlorine bleach have a significantly lower risk of developing asthma and of being sensitized to indoor allergens, especially house dust mite. These protective effects of chlorine bleach were observed in all categories of children regardless of gender, ethnicity, previous respiratory infections, parental history of allergic diseases, and even of their total serum IgE level. The only factor interfering with these effects was parental smoking, which abolished the protection given by the use of bleach against the risk of sensitization to indoor allergens, while increasing the risk of recurrent bronchitis through apparently an interaction with the use of bleach. Moreover, children living in a house regularly cleaned with bleach were less likely to have asthma (OR 0.10; CI 0.02–0.51), eczema (OR 0.22; CI 0.06–0.79), and of being sensitized to indoor aeroallergens (OR 0.53; CI 0.27–1.02), especially house dust mite (OR 0.43; CI 0.19–0.99). These protective effects were independent of gender, ethnicity, previous respiratory infections, total serum IgE level, and of family history of allergic diseases. They were, however, abolished by parental smoking, which also interacted with the use of bleach to increase the risk of recurrent bronchitis (OR 2.03; CI 1.12–3.66). House cleaning with bleach did neither show an effect on the sensitization to pollen allergens, nor on the levels of exhaled NO and of serum Clara cell protein and surfactant-associated protein D. House cleaning with chlorine bleach appears to protect children from the risks of asthma and sensitization to indoor allergens, while increasing the risk of recurrent bronchitis through apparently an interaction with parental smoking. As chlorine bleach is one of the most effective cleaning agent to be found, these observations argue against the idea conveyed by the hygiene hypothesis that cleanliness per se increases the risk of asthma and allergy.

A very good example on how multiple stressors in indoor environments affect human and more specifically children's health is the study carried out by Annesi-Maesano et al. (2012). The study aimed to provide objective assessments of IAQ to which young schoolchildren are exposed in classrooms, and to relate exposure to major air pollutants (chemical and biological) found in classrooms to asthma and allergies of schoolchildren. Based on this concept, a survey was conducted in a large sample of classrooms of primary schools in France, including schools in six cities (Bordeaux, Clermont-Ferrand, Créteil, Marseille, Strasbourg, and Reims) chosen for heterogeneity of air

pollution. Study participants were children aged 9-10 years who were invited to take part in a health survey according to a standardized protocol. Air pollutants were variously distributed in the sample. The lowest within-school (classrooms) variance was observed for acrolein (variance=2.55 µg/m³; SE=0.19 µg/m³; p<0.001) and the highest for formaldehyde (variance=183.52 mg/m³; SE=12.47 µg/m³; p<0.001), whereas the lowest between-school (schools) variance was observed for acrolein (variance=3.08 µg/m³; SE=0.53 µg/m³; p<0.001) and the highest for NO_2 (variance=107.26 µg/m³; SE=15.54 µg/m³; p<0.001). Overall, about one-third of the children were exposed to high concentrations of air pollutants according to standards indicated by WHO for $PM_{2.5}$ (10 µg/m³/year) and NO_2 (40 µg/m³/year). In some classrooms, very high concentrations were found for formaldehyde, $PM_{2.5}$ and NO_2. After adjusting for confounders, rhinoconjunctivitis was more frequent in classrooms with high formaldehyde concentrations, and asthma was more common in classrooms with high $PM_{2.5}$ and acrolein levels. The results are consistent after accounting for SES and ethnicity in the marginal models. Stratifying the population according to skin prick testing positivity showed that $PM_{2.5}$, acrolein, and NO_2 were significantly related to allergic asthma. In contrast, acrolein was negatively associated with non-allergic asthma. Taking into account the time of year when the survey was conducted (spring and summer: 227 classrooms, 3609 schoolchildren; autumn and winter: 175 classrooms, 2981 schoolchildren), the following significant associations were found: $PM_{2.5}$ and asthma (OR 1.28, 95% CI 1.00- 1.65), acrolein and asthma (OR 1.37, 95% CI 1.14-1.66) and $PM_{2.5}$ and allergic asthma (OR 1.41, 95% CI 1.16-1.73) during the warm season; NO_2 and asthma (OR 1.18, 95% CI 1.01-1.39) and FA and rhinoconjunctivitis (OR 1.41, 95% CI 1.08-1.85) during the cold season. Sensitivity analysis confirmed previous results, despite weaker statistical significance, probably because of the reduced sample size (data not shown). However, non-allergic asthma was found to be inversely related to acrolein (OR 0.36, 95% CI 0.29-0.44). The results were consistent after stratifying the restricted sample according to atopic status. Lastly, levels of $PM_{2.5}$ and acrolein in classrooms correlated positively with the prevalence of exercise-induced asthma, which was assessed simultaneously. The study is a good example on how exposure to multiple stressors in a common indoor environment affects the health status of the occupants. Although interactions between the stressors were not identified we should keep in mind that all these stressors are ubiquitous in indoor school environments and that all of them need to be taken into account when planning to improve IAQ.

Roussel et al. (2011) carried out an interesting study that describes how demographic differences within a country population correspond to health responses (allergies and asthma) not explained solely by levels of exposure (to moulds and actinomycytes). Several studies have suggested that children exposed to a farm environment are protected against allergies and asthma. The objectives were to determine and compare the fungi and actinomycetes present in farming and non-farming environments (children's bedrooms and cowsheds) and to identify the agricultural practices associated with an increase in airborne fungi and actinomycetes in cowsheds. The work presented herein (Roussel et al., 2011) is an environmental study nested within the PASTURE cohort in three regions of the Alpine Arc and includes 97 farmers (17 in the St. Gallen area, Switzerland;; 31 in the Franche-Comte district, France; and 49 in the Bavaria district, Germany) and 74 non-farmers (12 from Switzerland, 26 from France, and 36 from Germany). Air samples were collected by air pump and were analysed by culture and by direct counting of spores on membranes. The main micro-organisms observed in the cowsheds were also found in children's bedrooms. Among them, 13 were present in more than 97% of the samples: *W. sebi*, *Absidia* spp., *Aspergillus* spp. (*Eurotium* spp*., A. fumigatus, A. niger, A. versicolor, A. nidulans*), *Cladosporium* spp*., Penicillium* spp., yeasts, S*. viridis*, and mesophilic and thermophilic actinomycetes. During their stay in bedrooms, children living on farms were exposed to significantly greater amounts of *Absidia* spp., *Eurotium* spp., *Cladosporium* spp., *Penicillium* spp., and mesophilic actinomycetes than children who did not live on farms. These findings suggest that a part of the cowshed micro-flora is transported to the house indoor environment, leading to a moderate but continuous level of exposure to the cowshed bio-aerosol. Both the peaks encountered during the short stays in the cowshed and the moderate, but

continuous airborne micro-flora exposure in the bedrooms, should be taken into account when assessing microbial exposure assessment in the farming context. It is interesting that such environments are associated with a lower prevalence of asthma and atopic diseases. Farm exposure to moulds and actinomycetes plays a role in the modulation of immunity in humans. It is noteworthy that *Eurotium* spp., as well as several thermophilic actinomycetes, are known to be involved in immunological disorders, such as hypersensitivity pneumonitis. This includes farmer's lung disease, an occupational disease due to an inappropriate immune response in some farmers exposed to high levels of moulds and actinomycetes during hay handling (Roussel et al., 2004). Immunological disorders related to this condition are not fully understood, but they differ from atopic response, and mainly result in extrinsic allergic alveolitis, corresponding to alveolitis with granuloma formation and diffuse interstitial pneumonitis. The importance of the study relies on the identification of different immunizations arising from demographic-originated exposure variability; although farmer children are highly exposed to moulds and actinomycytes, their response to atopic diseases cannot be described by the concentration-response functions derived for non-farmer children living in urban settings.

Very interesting results in terms of combined exposure in indoor environments were derived by Sarigiannis et al. (2012). The study comprised an extensive review of the peer-reviewed literature (2001-2011) on BTEX concentrations in indoor locations within Europe, clustered by location, i.e. residences, workplace, schools, leisure facilities (bars, restaurants, museums) and transportation (tram, metros, buses), and integrating them within a database.

Results summarized in Table 2 show that individuals living in Europe are exposed simultaneously to multiple major organic compounds, however the levels, as well as the ratio between them, changes with geographic location. People living in the southern part of Europe are more exposed to all the compounds simultaneously with the exception of formaldehyde and, to a lesser extent, acetaldehyde. These two compounds generally exist in higher concentrations in northern European residential dwellings. This can be explained by two factors: different ventilation schemes between north and south (due to the differing climatic conditions resulting in lower air exchange between the indoor and the outdoor environment), and extended use of wooden furniture and building materials in the European north. Fuel- and solvent-related compounds, such as benzene and toluene, are up to two to three times more abundant in the indoor air in the south than in the north areas of Europe. This is a consequence of indoor sources, such as building materials and SHS, and outdoor sources such as transport. Outdoor sources have a much higher influence on indoor air concentrations in the south than in the north, due to the higher outdoor-to-indoor air penetration observed in the warm climate countries. Styrene and xylenes are also more abundant in the south even though their origin is more indoor-based. This can be explained primarily by the relative prevalence of cigarette smoking in the south compared to the north of Europe, even though building materials like carpets and parquet floor covering (which are significant sources of styrene and xylenes) are widely used in northern Europe.

Exposure was estimated based on detailed activity patterns (stratified by age), on the basis of time spent at the respective locations. Uptake was estimated based on diurnal variability of exposure, incorporating the effect of the activity type on inhalation rate. Uptake was used as input to a multicompartmental physiologically-based pharmacokinetic model of a quaternary mixture of VOC's (BTEX), which takes into account the interaction (i.e. competitive inhibition of metabolism) among the mixture constituents. The aim was to assess the BED in the target tissue (bone marrow) of the benzene metabolites (benzene oxide, phenol, and hydroquinone) associated with leukaemia. Model results were validated against human biomonitoring data of occupants exposed to benzene. The review process revealed large gaps in the concentration/exposure data necessary for a comprehensive Europe-wide exposure assessment study.

Table 2. Statistical overview of indoor concentrations recorded in residential settings in Europe

		Indoor pollutant levels (µg/m^3)		
		Mean	*Max*	*Min*
Formaldehyde	*North/Central*	**29.8**	*115.0*	*4.8*
	Southern	**12.7**	*32.9*	*5.2*
Benzene	*North/Central*	**3.1**	*7.0*	*0.3*
	Southern	**10.4**		
Acetaldehyde	*North/Central*	**13.0**		
	Southern	**11.2**		
Naphthalene	*North/Central*	**1.1**	*970.0*	
	Southern	**51.8**		
Toluene	*North/Central*	**20.6**	*43.6*	
	Southern	**53.1**		
Xylene	*North/Central*	**5.0**	*58.6*	
	Southern	**18.2**		
Styrene	*North/Central*	**1.1**	*4.8*	
	Southern	**8.1**		
α-Pinene	*North/Central*	**12.9**	*393.0*	
	Southern	**23.3**		

Note: North/central Europe includes Germany, United Kingdom, Northern France, Belgium, Denmark, Netherlands, Austria, Finland, Sweden; southern Europe includes Portugal, Spain, Southern France, Italy, Greece, and Cyprus

Source: Sarigiannis et al. (2012)

Additional data problems were revealed regarding the representativeness and quality of the measurements made. Wide differences were identified within the several indoor locations, the highest concentrations being related to transportation modes. Intra-country variability is larger than intercountry variability, reflecting the significance of local effects (e.g proximity to heavily traffic roads), as well as indoor sources (e.g. smoking) to indoor concentrations and, respectively, to exposure. In general, higher exposure levels were identified among south-eastern European countries, because ofto the significant contribution of the traffic component to emissions of aromatic compounds. Wider differences where identified in terms of benzene uptake within the several age groups. These differences are attributed to the higher bodyweight normalized dose for infants (0 to 2 years old) and children (3 to 9 years old) compared to adults (2.5 µg/kg bw/d vs. 1.8 µg/kg bw/d). These differences were further amplified in terms of BED (0.08 µg/L compared to 0.03 µg/L), indicating the increased leukemia risk for infants and children compared to adults for similar levels of environmental exposure. Inhibition of benzene metabolism due to co-exposure to TEX was initiated in indoor locations associated to elevated BTEX level (cumulative concentrations above 100 µg/m^3), modifying the overall BED. This, however, is a very rare case in common residential settings. In conclusion, this study had several outcomes: (a) it provided EU-wide data and assessments on indoor exposure to VOC and carbonyl compounds, (b) it delivered a mechanistic framework for taking into account the effect of multiple exposure on adverse health outcomes, and (c) it derived a method for translating differences in health responses between infants/children and adults to the same levels of environmental contamination.

Among the most comprehensive studies on the indoor school environment is the one carried out by Wallner et al. (2012) aiming to improve knowledge on air pollution in schools and its effect on the lung function of schoolchildren. The study followed a cross-sectional approach and assessed differences in indoor pollution in nine elementary all-day schools. 34 pollutants were analysed to identify a relationship with respiratory health determined by spirometry. In addition, the study used a linear regression model. Overall 596 children (aged 6–10 years) were eligible for the study. Spirometry was performed in 433 children. Indoor climate factors (temperature, humidity) as well as chemical factors were measured. The 252 chemical indoor air parameters comprised the following chemical families (number of compounds in each group is given in brackets): alcohols (2), chlorinated hydrocarbons (4), aromatic hydrocarbons (12), aliphatic hydrocarbons (13), terpenes (3), aldehydes (9), other relevant compounds including NO_2 (10), volatile compounds in PM/school dust (26), musks (5), phenols (19), phthalates (11), trisphophates (9), PAH (16), PCB (7), organophosphorous esters (7), organochlorine pesticides (22), other pesticides (3), polybrominated diphenyl ethers (20), organotins (6), metals (19), pyrethroids (12), inorganic components (8), industrial chemicals (3), disinfectants (1), caffeine and nicotine (2), and total, elemental and organic carbon (3). PM_{10} concentrations (daily mean values) in schools ranged from 2 μg/m^3 to 62 μg/m^3 (median: 29 μg/m^3), and $PM_{2.5}$ concentrations ranged from 1 to 34 μg/m^3 (median: 12 μg/m^3). CO_2 concentrations (1 hour-moving average) ranged from 350 to 3300 ppm. Regarding VOC and aldehydes, almost all compounds investigated were above the limit of quantification (LOQ). In more than three measurements, acetophenone (11 samples), n-decane (13 samples), and formaldehyde (3 samples) were above the 90th percentiles. Formaldehyde was found in concentrations ranging from 6.5 to 136.5 μg/m^3 (median: 29.8 μg/m^3). The levels of other relevant VOC were as follows: ethylbenzene (median: 1.5 μg/m^3, range: 0.5–10.3 μg/m^3); m-, p-xylene (median: 4.1 μg/m^3, range: 1.0–20.5 μg/m^3); and o-xylene (median: 1.5 μg/m^3, range: 0.5–7.3 μg/m^3). Within the group of trisphosphates, TBoEP (tris(2-butoxyethyl)-phosphate) was detected in the highest concentrations in school dust (median 2000 mg/kg), as well as in PM_{10} (median 1600 mg/kg) and $PM_{2.5}$ (2100 mg/kg). TDCPP (tris(1,3-dichlor-2-propyl)-phosphate) levels in PM_{10} ranged from <LOD to 4200 mg/kg (median 90 mg/kg) and in $PM_{2.5}$ from 29 to 16 000 mg/kg (median 164 mg/kg). DEHP median values in classroom dust, PM_{10} and $PM_{2.5}$ were 3350 mg/kg, 10 000 mg/kg, and 19 000 mg/kg, respectively. The median concentration of benzylbutylphthalate in school dust was 34 mg/kg (range: 14–500 mg/kg). Among the polybrominated diphenylethers, PBDE 209 showed by far the highest concentrations. Median values of PBDE 209 in school dust, PM_{10} and $PM_{2.5}$ were 600, 300, and 275 mg/kg, respectively. Only some of these pollutants, however, showed sufficiently high variation across schools to be entered into the analysis of an association with lung function parameters. Ethylbenzene, m-, p-xylene and o-xylene revealed significant negative correlations with forced vital capacity and forced expiratory volume in the first second. This was also true for tris(1,3-dichloro-2-propyl)phosphate (TDCPP) in PM_{10} and $PM_{2.5}$. In addition, formaldehyde indicated a significant negative correlation with maximal expiratory flow volumes. Although that study is the most comprehensive in terms of multiple exposure to chemicals, it could be more informative if air quality indicators were associated to a wider variety of health endpoints, or interactions between the several types of pollutants had been investigated.

7. Concluding remarks

7.1 Major health stressors in the indoor environment

The indoor environment is of key importance for human health and well-being, not only due to the time spent indoors during our life time span (approximately 90%), but also due to the combination of health and safety threats daily encountered. Prevalence of SBS is enhanced by the combined action of exposure to biological agents and chemicals or additional parameters related to thermal conditions and safety and satisfaction/discomfort. Insufficient housing conditions are strongly correlated with low SES.

Among the several health threats, exposure to multiple chemical agents still remains the silent threat: poor indoor environment quality (in terms of exposure to chemicals) is not always perceived by the occupants. As a result, occupants are continuously exposed to a cocktail of carcinogens (benzene, formaldehyde, PM-PAH) and endocrine disruptors (phthalates, PCB). The combined effects of these chemicals are still not sufficiently elucidated, since their physic-chemical and biochemical properties would favor multiple ways of interaction upon human uptake; there might be synergies in effect (e.g. PAH and nitrosamines of SHS, both causing lung cancer), or they might inhibit each other's metabolism – this is the case for the almost ubiquitous indoor BTEX mixture. In any case, although further investigation on the mechanisms elucidating mixture toxicity is needed, no significant departure from additivity in the health effect assessment was observed for the concentrations encountered usually in non-occupational settings.

In the absence of a comprehensive mechanistic frame for assessing cumulative exposure, cohort studies focusing on the investigation of evidence for synergies between different types of stressors (e.g. NO_2 and moulds in immune sensitization) are needed. However, transferability of these exposure-response functions needs to be done wisely; different background exposure levels of different population groups result in different responses to xenobiotics or biological agents for a given exposure increment. In addition, the same indoor environmental media concentrations might correspond to different exposure/intake patterns among the population, and these differences are potentiated when taking into account inter-individual differences on metabolism to xenobiotics.

7.2 Main sources

Besides the lack of quantitative knowledge on interaction mechanisms, there are significant data gaps in terms of assessing indoor environment quality. Data are collected using different sampling protocols (e.g. use of standard analytical techniques, survey design, standardized questionnaire, target locations period, and frequencies of measurements). This limits their direct comparability and data interpretation. In addition, data for emerging pollutants, such as phthalates and BFR, are available only in few countries. In terms of sources, indoor smoking contributes to significant increase of indoor concentrations regarding the mixture of CO, VOC, and PM. SHS is the most dominant parameter influencing indoor PM and BTEX concentrations, beyond the contribution of nearby traffic sources. Open combustion sources, such as cooking fires, result in high levels of PM and CO. In addition to the complexity of the overall indoor exposure, many commercial cooking exhaust devices manage to achieve capture efficiencies that approach or exceed 75% (i.e. 75% of emitted pollutants are captured by the exhaust device) only when operating at settings that produce prohibitive noise levels. Ambient ozone and its potential precursors, such as indoor styrene and frequent use of air fresheners, containing unsaturated volatile organic compounds (terpenes) result in increased concentration of aldehydes, which exacerbate adverse health effects such as respiratory allergies and asthma in susceptible individuals. Building materials and furnishings may be high in concentration of contaminants, which are released slowly when the indoor environment is acting as an effective chemical storage. Over the past 15 years, some chemical classes commonly used in

building materials, furnishings, and consumer products have been identified as endocrine disrupting chemicals – they interfere with the action of endogenous hormones (Rudel and Perovich, 2009). These include PCB, used in electrical equipment, caulking, paints and surface coatings; chlorinated and BFR, used in electronics, furniture, and textiles; pesticides, used to control insects, weeds, and other pests in agriculture, lawn maintenance, and the built environment; phthalates, used in vinyl, plastics, fragrances, and other products; alkylphenols, used in detergents, pesticide formulations, and polystyrene plastics; and parabens, used to preserve products like lotions and sunscreens.

Geographical disparities are observed between North and South Europe in terms of indoor exposure to health stressors in schools/kindergartens. For example, pollution levels in Greek schools/kindergartens show an average value of 5.33 $\mu g/m^3$ (3.1 $\mu g/m3$ – 7.8 $\mu g/m^3$) of benzene and 16.55 $\mu g/m^3$ (13.8 $\mu g/m^3$ – 20.2 $\mu g/m^3$) of formaldehyde. The same chemical compounds show average values in Dutch schools/kindergartens of 1.42 $\mu g/m^3$ (0.8 $\mu g/m^3$ – 3.0 $\mu g/m^3$) of benzene and 13.93 $\mu g/m^3$ (6.1 $\mu g/m^3$ – 22.4 $\mu g/m^3$) of formaldehyde. Indoor VOC and bioaerosol levels were found higher in primary school and kindergarten than other places of work. Geographic and socio-demographic gradients have also been found also in BTEX concentrations; the latter are always higher in suburban schools than city schools. Concentrations of formaldehyde are also lower in schools/kindergartens than in homes but in this case the difference is lower than for BTEX, implying that common emission sources such as construction products and furniture are present in both indoor setting types.Physical activity of pupils strongly contributes to the emission and re-suspension of particles; as a result, daily indoor PM_{10} levels have been found to frequently be higher than the levels outdoors, except on the weekends. The indoor concentrations of atmospheric aldehydes (formaldehyde, acetaldehyde, propionaldehyde, and benzaldehyde) have greater values as compared to those outdoors, particularly for formaldehyde, suggesting that indoor sources are more important contributors to the indoor pollution levels than outdoor sources such as infiltration of vehicle exhaust. Higher coarse particle fraction concentrations are observed at higher indoor air temperatures and CO_2 concentrations (Polednik, 2011), highlighting also that concentrations of small particle fractions are positively correlated with indoor air relative humidity. Reduction of exposure to noise is in contradiction to sufficient ventilation in classrooms (Mumovic et al., 2009). The occupants of the classroom (i.e. pupils and teachers) in noisy areas tend to shut windows, especially during quiet activities, resulting in increased likelihood of classrooms experiencing overheating during hot weather and poor air quality due to the lack of sufficient ventilation (Montazami et al., 2012). The needs for sufficient IAQ, lighting, thermal comfort and acoustic performance are mutually contradictory (Viegas et al., 2009). Studies in England have found that classrooms are often inadequately ventilated, with an increased risk of adverse impacts on the pupils (Mumovic et al., 2009) concluding that it was possible to achieve natural ventilation designs that met the criteria for indoor ambient noise levels when external noise levels were not excessive.

Infiltration factors are influenced by the micro-environment, ventilation type and air exchange rate, implying that indoor environments occupied by children offer little protection against outdoor combustion-related particles and gases. A study conducted on IAQ in 28 day care centers in Paris investigated biological contaminants (dust mite allergens, endotoxins, airborne fungi), chemical pollutants including aldehydes, VOC and NO_2, as well as temperature and relative humidity. For all VOC except benzene, indoor concentrations were higher than the respective outdoor levels; this might be due to VOC-emitting materials and activities including painting and the necessary hygienic cleaning schedule. However, because the law obligates day care centers to have an adequate ventilation system, the levels measured were lower in day care centers as compared to those measured in homes. Aldehyde concentrations in day care centers were lower than in dwellings. NO_2 levels, although lower than the outdoor ones, were higher compared to Paris homes, mainly due to the proximity to traffic roads and increased ventilation. Biological contamination was examined to show higher values in homes, which is explained by the penetration of outdoor contamination. Increased levels of endotoxins are due to high occupancy levels and frequent diaper changes.

Crowding is confirmed to be a determining parameter for IAQ and thermal comfort: in a study from Portugal, poor IAQ and thermal comfort in high school buildings was associated with high density of students in classrooms (Dias et al., 2011). Overcrowding of classes might overwhelm the building design specifications for sufficient IAQ and thermal comfort (Stankevica, 2011).

7.3 Exposure-health associations

Based on current knowledge, only limited associations between co-exposure to multiple health stressors and adverse health outcomes can be confirmed. Combined presence of indoor VOC and indoor use of insecticides in dwellings has been found to increase the relative risk of leukemia and lymphoma. Application of specific household chemicals might also have positive associations to specific health outcomes. Bleach is capable of inactivating allergens and its domestic use may reduce the risk of allergies in children. Although more frequent wet cleaning of surfaces and floors may contribute to a reduction of particle re-suspension, this is usually accompanied by the use of detergents; the latter have been found to be among the main contributors of xylenes and other VOC, which are related to reduced lung function, allergies, and asthma development. Regarding asthma, the most significant risk factors for adults were living in damp houses (OR 1.53; 95% CI 1.29–1.81) or in overcrowded houses (OR 1.35; 95% CI 1.05–1.75). Jackson et al. (2013) have reviewed seven risk factors for severe acute lower respiratory infections (ALRI) in children. Among housing conditions, crowding had an odd ratio of 1.96 (1.53-2.52) and exposure to indoor air pollution 1.57 (1.06-2.31). Crowding is a typical example of exposure to multiple risk as it is frequently associated with noise and inadequate hygiene standards, and inversely related to SES (Evans et al., 2010). Although households with more chaos are disproportionately likely to be socioeconomically disadvantaged, chaos is associated with poorer developmental outcomes for all children, regardless of SES. Children living in chaotic home environments have been found to exhibit poorer academic, socio-emotional, and self-regulatory outcomes. Studies have also demonstrated links between specific dimensions of chaos and young children's cognitive growth. For example, crowding in the home during infancy has been linked to poorer cognitive and communication skills (Evans et al., 2010).

Home exposure to biological factors results in neutrophilic airway inflammation, increasing the susceptibility to formaldehyde and toluene exposure. SBS was positively associated to the presence of specific MVOC emitted from airborne (mostly) or settled mould, formaldehyde, and the plasticizer texanol. In many dwellings elevated VOC concentrations were positively correlated to apartments with reported damages due to dampness; the latter is attributed to the intensification of VOC emissions from furniture and building materials. In this case, not only is there co-exposure to multiple factors (mould and VOC) resulting in a common adverse health outcome (asthma), but the presence of the one acts synergistically on the presence of the other. Assessment of combined exposure to particles of biological and chemical origin identified statistically significant (p <0.05) positive associations between particle mass and blocked nose, between total bacteria and both cough and blocked nose, between viable fungi and headache, as well as between viable bacteria and eye symptoms. However, the factors influencing IAQ differ on a seasonal basis: biological propagation is dominant in the winter, whereas penetration of particles from outdoor to indoor by ventilation is dominant in the summer.

In the school environment, negative associations were found between airflow in the lungs of schoolchildren and formaldehyde in the air, benzylbutylphthalate, and the sum of polybrominated diphenylethers in school dust. Moreover, ethylbenzene, m-, p-xylene, and o-xylene showed significant negative correlations with FVC (forced vital capacity) and FEV1 (forced expiratory volume in the first second), which represent key indices of compromised lung function at young age.

7.4 The way forward for action

Main challenges ahead. Comprehensive studies aiming to capture a wide spectrum of chemical, physical, and biological stressors existing in indoor environments and to evaluate an indoor environment as a whole in terms of potential health threats are lacking. Moreover, mitigation measures of large-scale environmental challenges, such as climate change, may pose additional risks for IAQ; the need for increased insulation in the interest of energy conservation protects from outdoor pollutant infiltration and traffic noise, however, it also enhances accumulation of pollutants emitted indoors, as well as the development of mould/damp. If combined with use of biomass (or, even worse, with the misuse of biomass which is linked to lower SES) for indoor space heating, then IAQ suffers from serious degradation.

A specific lack of information is identified in the area of home safety and injuries, which represents a major risk factor within buildings and causes a very significant health burden. Despite their acknowledged relevance, there is very little information on them vis-a-vis the other building-related risks, possibly because the identification and assessment of such hazards is difficult and based on rather different methods. Thus, the integration of home safety into integrated and holistic assessment of multiple exposure in built environments is to be considered a challenge for the future.

In general, lower SES is connected to lower indoor environmental quality, crowding, substandard hygiene, and disparities to health services. In the light of the current financial crisis and the increasing immigration pressure in many countries of the WHO European Region, the connection between SES of households and combined exposure to health stressors in the indoor environment risks to escalate if proper attention is not paid to this phenomenon.

What must be done? Considering the complexity of the multiple stressors encountered in indoor environments, the proper identification of the effects of combined/cumulative exposure among them requires:

- integrated analysis and assessment of indoor environment quality and other housing-related hazards, clustered by type of indoor setting;

- identification of potential synergies of stressors on a mechanistic basis, using the latest advances in *in vitro* testing and computational toxicology;

- confirmation of mechanistic hypotheses of action by comprehensive environment-wide association studies.

The identification of the critical points affecting exposure and the respective health outcomes will provide the framework for efficient interventions aiming at minimizing the health risks associated with non-occupational indoor built environments. Significant differences in the indoor environment health stressors profiles are observed across Europe, in terms of both inter- and intra-country variation. Only some of this variance can be explained by socioeconomic and demographic discrepancies, although more targeted studies are needed to fully comprehend these associations. Governments should support country- or region-specific targeted campaigns following harmonized protocols that include all potential risk factors (chemical, biological, physical, unhealthy, and unsafe housing) with respect to the specific geographic characteristics, including housing (e.g. building materials, furnishing, ventilation/insulation, means of space heating) and non-housing (traffic intensity and proximity, climate) factors. An ideal study in this direction would (a) include the multiplicity of risk factors included in e.g. the LARES survey (WHO Regional Office for Europe, 2007) and the spectrum of stressors analysed by Wallner et al. (2012), (b) associate exposure and outcomes as Hulin et al. (2010) did and (c) provide mechanistic confirmation (i.e. confirmation of the mechanisms of action) as described for BTEX, including toxicokinetics (Sarigiannis and Gotti, 2008) and in vitro analysis (Sarigiannis et al., 2009). Such a study needs to be longitudinal, representative of the targeted population, with data collected for an extensive time, and made available in the appropriate format to the scientific community. Examples of such initiatives include the NHANES

study of the US Center for Disease Control (CDC), the German Environmental Surveys (GerES), and the just started Health and Environment-Wide Associations via Large population Surveys (HEALS) in the EU.

In terms of combined indoor exposure, mitigation measures should focus on the minimization of the individual risk factors. Among the several risk factors, indoor combustion sources such as smoking and use of biomass for space heating are determinants of poor IAQ; although the continuous information to public has resulted in reduced smoking prevalence and indoor contamination by SHS, use of biomass for space heating is a growing concern. Tobacco smoke is considered as the most toxic chemical mixture, including most of the harmful compounds (especially the carcinogenic ones such as benzene, benzo[a]pyrene and other PAH, nitrosamines, and formaldehyde) found indoors. The same holds for indoor biomass burning, especially with regard to open fireplaces—these are strong emitters of PM and other combustion products such as CO and NO_2 and their use should be banned or proactively discouraged in cities. In-house storage of wood pellets should be avoided since it may result in high levels of hexanal and CO; it is postulated that the latter is formed through autoxidative degradation of fats and fatty acids (Wallner et al., 2012).

Considering that a vast majority of compounds is related to building materials (VOC and phthalates), furnishing (formaldehyde), household chemicals (VOC), and consumer products (BFR, phthalates), emissions from these products need to be kept at minimal levels. Use of product labeling should be encouraged and applied in particular for building materials, office, and electronic equipment, as well as furnishings. Bioclimatic architecture should be supported even with financial or fiscal incentives in order to facilitate attainment of thermal comfort and adequate ventilation avoiding indoor combustion sources and excessive energy consumption. In particular in schools and kindergartens, mechanical ventilation seems to be essential in ensuring adequate IAQ without increased noise levels in the class. Noise barriers along highly trafficked roads should be used to reduce the overall indoor noise burden, especially in areas with high density of schools/kindergartens and day care centers. Public procurement in terms of materials and equipment and consumer products used in these indoor settings should follow green procurement guidelines such as the ones outlined by the European Commission, with emphasis on the products coming to close contact/proximity to young children.

Emerging compounds such as BFR and phthalates are characterized by low volatility. Thus, they are found mostly in indoor dust. Non-dietary dust ingestion is considered as the dominant exposure pathway for children, who ingest about 10 times more settled dust (normalized for bodyweight) than adults. Therefore,, frequent dust removal is highly recommended in residential settings; methods of dry (electrostatic) removal are essential, since the use of wet cleaning is usually accompanied by the use of household chemicals. Alternative methods for reducing cumulative exposure to chemical include the use of common houseplants; a study by Pegas et al. (2012a) showed that common houseplants are useful in improving overall IAQ. After the placement of six potted plants in a classroom over an extensive indoor air measurement campaign, a significant reduction in CO_2, VOC, carbonyl, PM_{10}, organic carbon, nitrate, sulfate, ammonia, calcium, and carbonate concentrations was observed. The decrease in indoor air pollutant levels resulting from the use of plants may represent a low-cost solution to reduce exposure to many compounds and lifetime risk, and to further improve performance, attendance, and welfare of students and teachers in classrooms. This simple measure does not invalidate, however, the adoption of other abatement or preventive strategies, such as use of low-VOC-emitting materials and consumer products, lowering the occupancy rates in classrooms, use of air cleaner and humidity control systems, and increasing the ventilation rates (through natural openings or mechanical devices).

Home safety is a leading cause of death and disability for both the young and the elderly and is a real housing issue that cannot be ignored. It needs to be addressed by measures that increase the awareness of the public regarding the importance of home safety and injury avoidance through

practical and architectural solutions, and remove or reduce the health risks that endanger home safety. Such risks include low SES, crowding in dwellings, and negligence in building maintenance.

How can such data help governments to protect the population? The data collected and reviewed in this report are intended to support policy-makers investigating the impact of combined/multiple exposure on population health by identifying:

- which are the most dangerous and frequent stressors encountered in indoor environments, categorized by type of setting (residential dwellings, schools/kindergartens, and day care centers);

- which are the most important and intense emission sources;

- which are the most frequent combinations of risk exposure; and

- which are the gaps of evidence that have to be addressed.

The report describes the way combined exposure to chemical and biological agents in the indoor environment may result in modification of the risk of adverse health effects. This knowledge can be essential in designing adequate public health protection policies taking into account socioeconomic, geographic, and demographic factors modifying population exposure and consequent health risk.

How can this information facilitate policy-making? The information gathered in this report can facilitate policy-makers and public health authorities to identify the appropriate countermeasures to limit co-exposure to such stressors taking into account the target population with the given socioeconomic and demographic disparities, as well as geographical differences that modify health risk. Reduction of indoor exposure to chemical, physical, and biological stressors requires a complex combination of public health policies and protective measures.

Evidence has shown that those who have the least resources at their disposal suffer the worst housing conditions. Policies should therefore aim to address social inequalities and protect low-income individuals who are more exposed to harmful stressors. Dealing with poverty will, thus, remain a most important element in any housing policy, either through specific housing programmes or through targeted economic policies. In addition, different policy priorities could be adopted for different geographical locations. For example, absence of basic equipment inside the home, as well as accessibility and affordability of drinking-water are more common in the new EU Member States and have considerable health consequences. For these countries housing policies should ensure that all new residences in public buildings or private houses offerbasic commodities.

What are the main evidence bits that would enable such policy-making? Comprehensive and harmonized data on combined exposure to chemical, physical and biological stressors in the indoor environment would be essential for public authorities responsible for public health protection. This report, based on a systematic review of the relevant literature over the last eight years, suggests that a new paradigm in public risk assessment should be followed by policy-makers who would need to focus not only on the risks posed to the population by individual stressors, but rather on the actual modification of the risk attributed to the combined exposure to the stressors taking into account socioeconomic and demographic differences. The evidence that would enable effective policy-making in this field includes:

- Levels of indoor stressors and identification of settings leading to co-exposure to multiple stressors, especially for susceptible population subgroups such as young children, pregnant women, and the elderly or individuals with prior health conditions rendering them more vulnerable.

- Identification of the links between building conditions and socioeconomic, demographic, and geographic risk modifiers.

- Evidence of adverse health outcome exacerbation by the synergistic action of several stressors to which population is exposed simultaneously.

- Relative prioritization of indoor health stressors with regard to burden of disease and frequency of combined exposure in dwellings, schools/kindergartens and day care centers.

- Identification of knowledge gaps.

In conclusion, the generation of policy-relevant data represents a key objective of this report in order to improve the knowledge of policy-makers and public health authorities on: (a) policy choices related to housing conditions, and (b) health-related consequences. More transparent and evidence-based data will help sharpen actions aiming at public health protection form indoor health stressors at the local, regional, national, and international levels.

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Annex 1: Combination of search terms of the extended literature survey

The following table presents the results of the extended literature survey undertaken in this frame of this study.

Table 3. Combination of search terms

Combination of search terms	Total publications identified	Publications matching criteria
Indoor pollution + insecticides	63	4
Indoor pollution + pesticides	104	12
Indoor pollution + biocides	9	3
Indoor pollution + disinfectants	48	9
Indoor pollution + detergents	28	2
Indoor pollution + accidents	57	3
Indoor pollution + harmful buildings	6	0
Indoor pollution + safety threats	0	0
Thermal conditions + dampness	2	0
Thermal conditions + damp	8	0
Thermal conditions + household chemicals	2	0
Thermal conditions + mould	151	0
Indoor pollution + aldehydes	148	8
Indoor pollution + VOC	169	17
Indoor pollution + SVOC	11	1
Indoor pollution + phthalates	45	6
Indoor pollution + flame retardants	125	16
Indoor pollution + PCB	18	3
Indoor pollution + ETS*	26	1
Indoor pollution + PM	107	20
Indoor + particulate matter + houses	72	9
Indoor + particulate matter + residential	86	11
Indoor + particulate matter + domestic	27	2
Indoor + particulate matter + day care	4	0
Indoor + particulate matter + schools	133	25
Indoor + particulate matter + classrooms	20	1
Indoor + crowding	40	2
noise + crowding	54	3
Indoor pollution + injuries	67	2
Indoor pollution + dermal	19	1
Indoor pollution + respiratory	755	19
Indoor + particulate matter + day care	4	0
Indoor + particulate matter + schools	133	25
Indoor + particulate matter + classrooms	20	1
Indoor pollution + Polycyclic aromatic hydrocarbon (PAH)	219	13
Indoor pollution + volatile organic compound + house	63	7
Indoor pollution + volatile organic compound + residential	48	4
Indoor pollution + volatile organic compound + household	35	0
Indoor pollution + volatile organic compound + dwelling	10	0
Indoor pollution + volatile organic compound + school	53	2

Indoor pollution + volatile organic compound + kindergarten	3	0
Indoor pollution + volatile organic compound + class	3	0
Indoor pollution + volatile organic compound + classroom	0	0
Indoor pollution + volatile organic compound + daycare	0	0
Indoor pollution + Social	197	9
Indoor pollution + socioeconomics	102	4
Indoor pollution + incomes	69	0
Indoor pollution + poverty	67	0
Domestic accidents (Article Title, Abstract, Keywords)	865	4
Domestic hygiene (Article Title, Abstract, Keywords)	559	4
Residential hazards + socioeconomic status (All Fields)	713	5
Indoor pollution + socioeconomic status (Article Title, Abstract, Keywords)	105	4
Indoor pollution + socioeconomic disparities (Article Title, Abstract, Keywords)	20	0
Noise + crowding (household chaos – PubMed)	97	3
Building + Health risk (Article Title, Abstract, Keywords)	3591	19
Home + Health risk	3796	26
Residential + Health risk	1276	12
Housing + Mortality	335	4
Cumulative indoor exposure	113	7
Cumulative indoor risk	91	6
Combined indoor exposure	245	13
Combined indoor risk	204	11

* As indicated by the table, the search term "environmental tobacco smoke" (ETS) was used to search for studies covering the impact of passive exposure to tobacco smoke. However, in the report, the term "second-hand smoke" (SHS) is used.

Annex 2: Combined exposure to health stressors in indoor settings

Residential buildings

Chemical mixtures/indoor pollutants

As part of an environmental investigation included in the PARIS birth cohort, ozone contribution to airborne aldehyde formation in Paris homes was examined (Rancière et al., 2011). Formaldehyde, acetaldehyde, hexaldehyde, styrene, nitrogen dioxide, and nicotine concentrations, as well as comfort parameters and carbon dioxide levels, were measured twice during the first year of life of the babies. Stepwise multiple linear regression models were used to link aldehyde levels with ambient ozone concentrations and a few aldehyde precursors involved in oxidation reactions, adjusting for other indoor aldehyde sources, comfort parameters and traffic-related nitrogen oxides. The study found a 4% and 11% increase in formaldehyde and hexaldehyde levels when 8-hour ozone concentrations increased by 20 $\mu g/m^3$. Results also revealed the influence of potential precursors, such as indoor styrene level and frequent use of air fresheners, containing unsaturated volatile organic compounds (e.g. terpenes), suggesting that ambient ozone can significantly impact IAQ, especially regarding formaldehyde and hexaldehyde levels.

In Stockholm (Sweden) benzene, 1,3-butadiene, benz(a)pyrene, NO_x and NO_2 were measured at homes and at two reference sites (urban background/traffic site) during September–December 2009 (Yazar et al. 2011), aiming to investigate whether the air pollution levels had decreased since the last assessment six years earlier, and to compare personal exposure levels (one-week average) and indoor levels with levels at outdoor reference sites. The (mean) personal exposure levels to benzene (2.5 $\mu g/m^3$) and 1,3-butadiene (0.5 $\mu g/m^3$) were higher than the levels associated with traffic (1.5 and 0.2 $\mu g/m^3$) and urban background (0.8 and 0.09 $\mu g/m^3$).

Another study done in Athens, Greece, analysed indoor air pollutants measuring the concentrations of CO_2, CO, total VOC (TVOC), $PM_{2.5}$, and PM_{10} in 50 residences (Santamouris et al., 2007). In addition, the ventilation rate in each dwelling was continuously measured by monitoring CO_2 concentration. The mean concentration of the $PM_{2.5}$ was approximately 82.5 $\mu g/m^3$, while the mean concentration of the PM_{10} was approximately 204.5 $\mu g/m^3$. For the PM_{10}, only 16% of the dwellings presented a concentration below the threshold value of 65 $\mu g/m^3$. For $PM_{2.5}$ almost 24% of the dwellings present a concentration below 50 $\mu g/m^3$, while 64% are below 100 $\mu g/m^3$. The ratio between $PM_{2.5}$ and PM_{10} varied between 0.2 and 0.8. The median concentration of $PM_{2.5}$ for dwellings without smokers was 62 $\mu g/m^3$, but increased to 80 $\mu g/m^3$ when smoking levels below 20 cigarettes/day were reported. For higher smoking levels such as 20-40 cigarettes/day and 40-80 cigarettes/day, the corresponding concentrations rise up to 97 and 116 $\mu g/m^3$, respectively. Concerning PM_{10}, dwellings without smokers present a median concentration of 129 $\mu g/m^3$. The concentration revealed higher values up to 153 $\mu g/m^3$ when smoking levels were below 20 cigarettes/day. The median ventilation rates for the smoking and the nonsmoking dwellings were 0.74 and 0.52 respectively.

In Barcelona (Spain), a study investigated the relationship between personal exposure to NO_x, NO_2, $PM_{2.5}$ and absorbance as a marker for black carbon in pregnant women, and the indoor and outdoor concentration levels at their residence (Schembari et al., 2013). Levels of personal exposure to $PM_{2.5}$ were slightly higher than indoor and outdoor levels (geometric mean of 26.2 $\mu g/m^3$ for personal exposure vs 23.1 $\mu g/m^3$ indoor vs 19.8 $\mu g/m^3$ outdoor). Overall NO_2 exposure accounted for astatistically significant associations with several housing parameters such as ventilation, type of cooking appliances, and proximity to intense traffic. Personal exposure to PM was correlated to parameters related to traffic fumes (time spent walking or biking together with the time spent outdoor) showing the lack of significant indoor $PM_{2.5}$ sources.

A study in Stockholm (Sweden) measured the effect of air exchange rate and human activity on $PM_{2.5}$, soot, and NO_2 during winter and summer indoors and outdoors at 18 homes (Wichmann et al., 2010). Indoor environments were free of SHS and gas appliances, as the aim was to assess to what extent $PM_{2.5}$, soot, and NO_2 infiltrate from outdoors to indoors. The median indoor and outdoor $PM_{2.5}$ levels were 10.0 μg/m³ and 9.8 μg/m³, respectively, and the median indoor/outdoor ratio was 1.12. This very high indoor/outdoor ratio was attributed to the use of inefficient filters in the ventilation system, since no significant indoor emission source was characterized as statistically significant.

A Danish study analysed CO and $PM_{2.5}$ in two reconstructed farmhouses (17-19th century) during two weeks of summer (Ryhl-Svendsen et al., 2010). During the first week, intensive measurements were performed while test cooking fires were burned; during the second week, the houses were monitored while occupied by guest families. During the first week the concentration of $PM_{2.5}$ averaged daily between 138 and 1650 μg/m³ inside the hearths and 21-160 μg/m³ in adjacent living rooms. CO averaged daily between 0.21 and 1.9 ppm in living areas, and up to 12 ppm in the hearths. Highest concentrations were measured when two fires were lit at the same time, which would cause high personal exposure for someone working in the kitchens. 15-minute averages of up to 25 400 μg/m³ ($PM_{2.5}$) and 260 ppm CO were recorded. On average, guest families were exposed to CO not exceeding 0.21 ppm CO during 48h.

An interesting study showing the complexity of different parameters that compose IAQ was conducted by Saraga et al. (2010), including $PM_{2.5}$, PM_1 and BTEX parallel indoor and outdoor measurements with and without the presence of SHS. The study concluded that the final indoor concentrations and the indoor/outdoor ratio are affected by outdoor air penetration and the presence of strong indoor sources, since both PM and BTEX originate from combustion sources (in this case smoking). As a result, indoor PM concentrations were twice as high compared to the outdoor ones in the smoker house, while indoor BTEX concentration was about 20% higher than the respective outdoor value. For the non-smokers house, differences between indoor and outdoor air concentrations of both PM and BTEX were almost negligible, showing that outdoor air quality was the most relevant determinant.

Two similar studies focused on the combined effect of a group of compounds well known for their carcinogenic potential (PAH) due to the presence of SHS (Castro et al., 2011a; Slezakova et al., 2009). PAH were determined in both gaseous and particles phase. The presence of SHS increased the content of PAH significantly in both phases, and lung cancer risk for non-smoking occupants living in the house with a smoker seemed to be significantly elevated compared to the residents living with non-smokers (4.1 10^{-3} and 1.7 10^{-3} respectively).

In Romania, a study assessed the levels and specific profiles of several organohalogenated contaminants, including organochlorine pesticides, PCB, and flame retardants – such as PBDE, hexabromocyclododecanes (Dirtu et al., 2012), novel BFR, and organophosphate flame retardants – in 47 indoor dust samples collected in 2010 from urban locations from Iasi, Eastern Romania. The dominant contaminants found in the samples were organophosphate flame retardants (median sum 7890 ng/g), followed by organochlorine pesticides (median 1300 ng/g). Except for BDE 209 (median 275 ng/g), PBDE were present in dust samples at relatively low levels (median sum PBDE 8 ng/g). PCB were also measured at low levels (median sum PCB 35 ng/g), while novel BFR were occasionally detected, indicating low usage of PCB in products present on the Romanian market.

Finally, in the review of exogenous environmental factors that may play a more important role in carcinogenesis, Belpomme et al. (2007) included chemicals related to indoor air and several household chemicals (formaldehyde, VOC such as benzene and 1,3 butadiene, nitrates, pesticides, organochlorines) among others. However, application of specific household chemicals might also have positive associations to specific health outcomes. Bleach is capable of inactivating allergens, and there associations were found that its domestic use may reduce the risk of allergies in children

(Zock et al., 2009). The use of bleach was associated with less atopic sensitivity OR 0.75; 95% CI 0.63-0.89). Dose-response relationships (P <.05) were apparent for the frequency of bleach use and sensitization rates. Lower respiratory tract symptoms, but not allergic symptoms, were more prevalent among those using bleach 4 or more days per week (OR 1.24-1.49). Although more frequent wet cleaning of surfaces and floors may contribute to a reduction of particle resuspension, this is usually accompanied by the use of detergents; the latter have been found to be of the main contributors of xylenes and other VOC, which are related to reduced lung function (Wallner et al., 2012), as well as allergies and asthma development (Billionnet et al., 2011).

The comprehensive review of Sarigiannis et al. (2011), covering studies published within the last twenty years (1990-2008), summarized data on the occurrence of major organic compounds. The review focused on various indoor environments in Europe revealing significant differences in IAQ levels within and among the countries where data were available.

Combined exposure data disaggregated by country shows wide variations in the levels of all compounds considered. The profile of combined exposure to major organic compounds in residential dwellings in the North/Central and Southern countries of Europe is summarized in Figures 6 and 7. Overall, people living in Southern countries are exposed at home to about twice as high concentrations of total organic compound as people living in northern or central Europe.
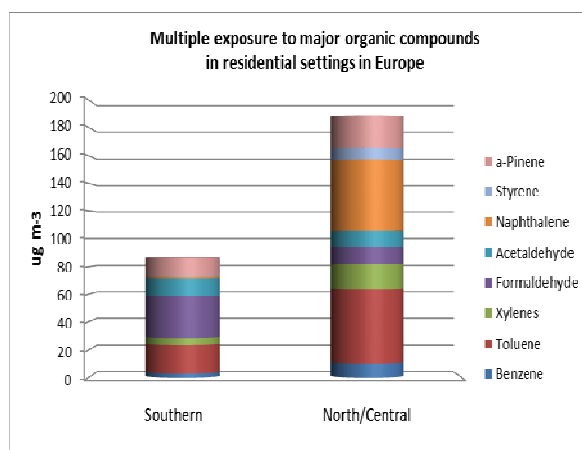

Fig. 6. Multiple exposure to major organic compounds in residential settings in Europe

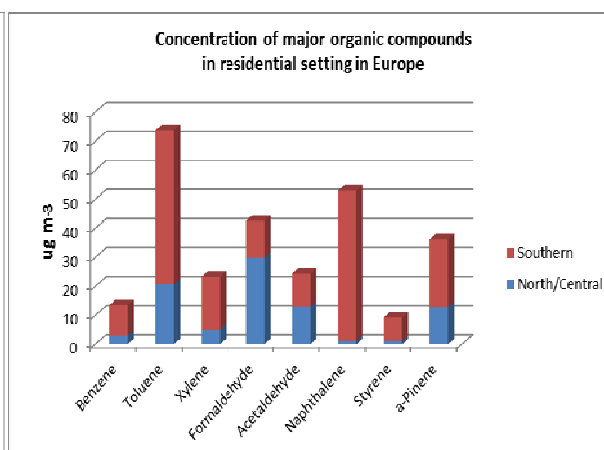*Source: Sarigiannis et al (2011)*

Fig. 7. Concentration of major organic compounds in residential settings in Europe

Source: Sarigiannis et al (2011)

For example, concentration data of toluene, benzene and limonene in similar residential settings in Greece (i.e. residential dwellings) show average concentrations values that are from one to five times as high as the ones in Finland. Dwellings had the same concentrations of xylenes in both countries. Styrene, α-pinene, formaldehyde and acetaldehyde were much higher in Finland than in Greece. Naphthalene was found practically only in Greece due to the use of mothballs (Table 4).

Chemical, biological, and physical stressors

Up to now there are very few studies dealing with exposure to multiple stressors and the related risks in indoor residential environments. Among these studies, the most comprehensive is the one carried out by Billionet et al. (2011); this study looked at 30 physical, chemical, and biological pollutants using data from a population-based representative sample of French dwellings with a specific sampling strategy for each pollutant (e.g. equipment, protocols for fitting, sample collection, analysis, room used). These pollutants contained 20 VOC, including 4 aldehydes, 12 hydrocarbons, and 4 glycolethers, 4 common allergens (dust mite allergens (Derp1 and Derf1), dog and cat (Canf1and Feld1)), CO, temperature, relative humidity, CO_2, PM, and radon. The study investigated the effects of exposure to various VOC, and considered their combined effect on adult asthma and

Table 4. Comparison of VOC levels in residential dwellings between Greece and Finland

All units in µg/m³	Greece			Finland		
	Mean	*Max*	*Min*	*Mean*	*Max*	*Min*
Benzene	10.1			2.15	2.2	2.1
Toluene	49.17	82.7	15.63	16.28	20.1	5.0
Xylenes	30.4			27.53	72	4
Styrene	0.94	1.9	0.08	2.03	3	1.1
Limonene	44.65	78.3	11.0	18.97	30.7	12
α-pinene	10.7			37.9	61	15.7
Naphthalene	83.5			0.5	0.6	0.4
Formaldehyde				26.78	41.4	19
Acetaldehyde	9.81			18.2		

Source: Sarigiannis et al (2011)

rhinitis. VOC concentrations were differently distributed in the 490 dwellings. Formaldehyde accounted for the highest median and 3rd quartile concentrations (19.4 and 28.3 µg/m³ respectively). The median concentrations of the single VOC, other than aldehydes measured in this study, were below 6 µg/m³ except for toluene. Correlation coefficients between VOC ranged between 0.15 and 0.96. The highest correlations were observed between acrolein and acetaldehyde (0.72), benzene and ethylbenzene (0.65), and benzene and m/p-xylene (0.63). The 77 dwellings not included in the present analysis differed from the 490 dwellings included in that they had 9 VOC of significantly higher concentrations than in the 490 dwellings. Inclusion of each binary VOC independently in a marginal model adjusted for confounders revealed that n-undecane and 1,2,4-trimethylbenzene were significantly associated with asthma with ORs of 2.02 (95% CI 1.18–3.46) and 2.10 (95% CI 1.21–3.65), respectively. No other significant relationships were discovered. The adjusted marginal model highlighted a significant positive association between asthma and the global VOC score, with an OR of 1.07 (95% CI 1.00–1.13), i.e. a risk of disease 1.07 times higher for 1 additional VOC with a high exposure level. Asthma risk was increased by 40% for five additional VOC with a high exposure level. The marginal model stratified on sex showed no significant difference in the global VOC score effect between male and female. Two specific VOC scores were significantly associated with an increasing risk of asthma: aromatic hydrocarbons (OR 1.12; 95% CI 1.01–1.24) and aliphatic hydrocarbons (OR 1.41; 95% CI 1.03–1.93). Moreover, when considering each VOC independently, ethylbenzene, trichloroethylene, m/p-, and o-xylene were significantly related to rhinitis after adjusting for confounding variables with ORs of 1.48 (95% CI 1.09–2.02), 1.54 (95% CI 1.07–2.21), 1.46 (95% CI 1.07–2.00), and 1.43 (95% CI 1.03–1.99), respectively. The strengths of this survey comprised of the use of a large population-based sample of dwellings selected by a random process and the inclusion of a broad range of VOC quantitatively assessed. However, no interaction among the individual compounds was investigated.

In France, Hulin et al. (2010) conducted a comprehensive study focusing on the comparison between urban and rural houses on childhood asthma development. The study included two case–control populations, composed of children living in the city (32 asthmatics and 31 controls) and in the countryside (24 asthmatics and 27 controls). Environmental monitoring included indoor assessment of NO$_2$, PM$_{2.5}$ and various VOC. Indoors, the highest median concentration was found for toluene (20.2 µg/m³ with a maximum of 522.5 µg/m³) followed by formaldehyde (19.2 µg/m³ with a

maximum of 75.1 µg/m^3). Median concentrations of PM$_{2.5}$, NO$_2$, and acetaldehyde accounted for approximately 10 µg/m^3. Benzene concentration was significantly lower (median concentration: 1.8 µg/m^3). Differences in indoor exposure were observed according to season. The study also measured higher concentrations of nitrogen dioxide and benzene in homes during winter season compared to those during summer season. Moreover, children living in urban areas were more exposed to indoor pollution than those in rural areas. Exposure to all measured pollutants, except acetaldehyde and xylenes, was significantly higher in the city. Concentrations almost twice as high were found in town compared to the countryside for all BTEX. A two to threefold increased risk of asthma was significantly associated with high exposure to toluene and acetaldehyde (OR 2.73; 95% CI 1.28–5.83, OR 2.15; 95% CI 1.01–4.58, respectively). No significant OR was found between asthma and exposure to NO$_2$ or PM$_{2.5}$. As interaction terms between exposure and location and season were significant for some pollutants, results were presented according to these factors. A six-fold increased risk of asthma was found among children highly exposed to toluene (OR 6.64; 95% CI 2.03– 21.78) during the winter campaign. Such association was not observed during the summer measures. On the contrary, high exposure to NO$_2$ in winter was negatively associated with asthma. Differences in the associations were also observed according to location; the ORs of asthma were significantly higher than 1.0 for elevated exposure to formaldehyde and toluene in the case of rural homes (OR 10.7; 95% CI 1.69–67.61 and 3.8; 95% CI 1.24-11.77 respectively), while in urban homes, these associations were not significant.

A study on dwelling pollution carried out in 567 primary residences in France in the period from October 2003 and December 2005 analysed combined exposure in homes (Duboudin, 2009); the sample was intended to be representative of the 24 million primary residences in continental France. The study summarizes the correlation between different types of chemical families through three methods of multidimensional descriptive statistical analysis in order to explore the correlations between the concentrations of the 18 VOC considered. Other chemicals (CO, CO$_2$, PM$_{2.5}$ and PM$_{10}$), physical factors (temperature, relative humidity), gamma radiation and radon, as well as biological stressors (cat, dog and dust mite allergens) were also considered in the analysis. Four groups of VOC were moderately or closely correlated to each other based on Spearman correlation. All correlation scores were greater than 0.4. The first group of closely correlated VOC consisted of aromatic hydrocarbons (mostly ethylbenzene, m+p-xylene and o-xylene), showing Spearman correlation scores from 0.92 to 0.96. Adding toluene, 1,2,4-trimethylbenzene and benzene lead to a correlation score ranging from 0.56 and 0.63. The second group of VOC identified was the aliphatic hydrocarbon group: n-decane and n-undecane, which together had a Spearman's correlation score of 0.82. This second group was correlated to 1,2,4-trimethylbenzene from the first group at values between 0.57 and 0.61, then linked to the quartet composed of ethylbenzene, m+p-xylene, o-xylene and toluene with correlation scores between 0.4 and 0.45. The third group of VOC identified was the aldehyde group. It was composed of acrolein and acetaldehyde, which were correlated with an initial score of 0.75, formaldehyde and hexaldehyde were then added, with a slightly lower correlation (0.56). The fourth and last group identified was made up of two halogenated hydrocarbons, trichloroethylene, and tetrachloroethylene, correlated to each other with a value of 0.5. The correlation scores between this group and the three previous ones are less than 0.4. Three VOC were relatively independent of one another and of all the others: 1.4-dichlorobenzene (which in some ways is similar to the two other halogenated hydrocarbons), 2-butoxy ethanol (in some way similar to the aldehydes), and 1-methoxy-2-propanol. These VOC did not show any correlation with any pollutant at a score higher than 0.4, except for the correlation of 2-butoxy ethanol with hexaldehyde (0.42). The least correlated VOC was 1-methoxy-2-propanol. The significant correlation scores found demonstrated that combined exposure to the investigated VOC is very likely in most of the 567 primary residences investigated. Moreover, this could be attributed to the presence of common indoor sources for many of these VOC and in particular for each of the four families identified. Combined exposure to different aromatic hydrocarbons was widely observed and somewhat similar correlation scores were also found for aliphatic hydrocarbons and to a lesser

extent for aldehydes and halogenated hydrocarbons. Some moderate cross-family correlations were also found (e.g. aliphatic hydrocarbon group and 1,2,4-trimethylbenzene), while the correlations between the other indicators measured were low compared with the correlations among VOC. However, several particularly low correlations should be noted: between the concentration of dust mite allergens (Der p 1) and relative humidity, and between the mean concentrations of CO and $PM_{2.5}/PM_{10}$. The correlations between the VOC and the other indicators were also low, e.g. $PM_{2.5}$ and PM_{10} were only slightly correlated to acrolein and acetaldehyde.

Haverinen-Shaughnessy et al. (2007) evaluated the combined effect of exposure to biological and non-biological particles in Eastern Finland including 81 randomly selected elementary school teachers. Sample collection was performed using personal and microenvironmental sampling from homes, and an 8-h sample collection was performed from workplaces of the studied subjects. The assessment of combined exposure to biological and chemical origin particles identified statistically significant ($p < 0.05$) positive associations between particle mass and blocked nose, between total bacteria and both cough and blocked nose, between viable fungi and headache, as well as between viable bacteria and eye symptoms.

A study carried out in Ankara, Turkey (Mentes et al., 2012) identified bioaerosol levels and species, VOC levels, and $PM_{2.5}$ levels in four different environments (house, office, kindergarten, and primary school), performing outdoor sampling in parallel. Air pollution samplings were carried out in each environment during five subsequent days in both winter and summer. The results indicated that bioaerosol, VOC, and $PM_{2.5}$ levels were higher in the winter than in the summer. Moreover, $PM_{2.5}$ and bioaerosol levels showed remarkable daily and diurnal variations, whereas a good correlation was found between the VOC levels measured in the morning and in the afternoon. The diurnal $PM_{2.5}$ variation was associated to wet cleaning applications, ventilation, and other human activities. Bacteria levels were, in general, higher than fungi levels. Among the VOC, toluene was the most predominant, whereas elevated n-hexane levels were also observed in the kindergarten and the primary school, probably due to the frequent wet cleaning during school days. Remarkable VOC levels were found in the kindergarten and the primary school giving rise to concern because of potential health risk for children. Several factors were found to be significantly influencing IAQ, and amongst them, VOC-based products used indoors ranked first. The relative importance of the different factors influencing IAQ showed significant seasonal variation. In the winter, the main contribution to IAQ came from bioaerosols and VOC, originating mainly from indoor sources. Solvent consumption results in high loadings of TVOC throughout the year. However, subsequent factors influencing IAQ differ on a seasonal basis: biological propagation is dominant in the winter, whereas penetration of particles from outdoor to indoor by ventilation is dominant in the summer; the latter was the factor least affecting the IAQ in the winter.

In three North European cities (Reykjavik, Uppsala, and Tartu), the combined effect of MVOC (from mould presence), formaldehyde and the plasticizers texanol and TXIB was evaluated against the prevalence of SBS in a study concucted by Sahlberg et al. (2013). From the study it was found that SBS syndrome was positively associated to the presence of specific MVOC emitted from airborne (mostly) or settled mould, formaldehyde, and the plasticizer texanol. These results are in agreement with the mechanistic hypothesis that exposure to biological factors results to neutrophilic airway inflammation, increasing the susceptibility to formaldehyde exposure (Hulin et al. 2010).

Schlink et al. (2010) evaluated the interaction between common housing conditions (such as selected building materials, ventilation, and recent renovation), presence of mould/dampness and SHS against the indoor levels of VOC in Leipzig, Germany. Taking smoking into account as a known source of several VOC, it is important to note that in many dwellings elevated VOC concentrations were positively correlated to reported moisture damage; attributed to the intensification of VOC emissions from furniture and building materials in damp homes. In this case, not only there is co-exposure to multiple factors (humidity, mould, and VOC) resulting in a common adverse health outcome (asthma), but the presence of one factor acts synergistically to the other. Large

international multicenter studies have shown significant differences between regions with respect to prevalence and severity of asthma and allergies. In a multitude of studies (Zuraimi et al. 2006) from different countries, adverse health effects among children have been associated with exposure to dampness in homes. Since countries differ in climate, culture, socioeconomic factors, housing characteristics, and indoor air pollution sources, these diversities are likely to cause important differences in exposures to dampness, as identified from studies in three different countries and climates (Sweden, Bulgaria, and Singapore). Several studies have suggested that children exposed to farm environments are protected against allergies and asthma. The study carried out by Roussel et al. (2011) within the PASTURE cohort in three regions of the Alpine Arc (Switzerland, France, and Germany) determined and compared the fungi and actinomycetes present in farming and non-farming environments (childrens bedrooms), identifying that farm children were also exposed to significantly greater amounts of *Eurotium spp.*, *Absidia spp.*, *Cladosporium spp.*, *Penicillium spp.*and mesophilic actinomycetes in their bedrooms than the non-farm controls. However, these environments are associated with lower prevalence of asthma and atopic diseases, confirming that populations with high microbial agent levels present lower sensitization rates, shifting down the dose-response curve between mite allergens and asthma and atopic diseases (Schram-Bijkerk et al., 2006). An international study of biocontaminants measured in house dust conducted in the Netherlands, Germany, and Sweden (the AIRALLERG study) showed that the within-home variance was small compared to the between-home variance for most variables (mostly less than half) with the exception of glucan on mattresses (Giovannangelo et al., 2007b).

Improving residential IAQ in terms of mould and dampness exposure is greatly facilitated by environmental home inspection services in western Europe provided for patients at the request of attending physicians to improve patient management (Charpin et al., 2011). The visit includes a standardised questionnaire as well as environmental sampling such as mite-allergen measurement, mould identification, and VOC measurements (Charpin-Kadouch et al., 2007). IAQ in terms of mould and dampness is improved by the use of transportable cleaning units with high-efficiency ozonizing, which is in most cases effective in decreasing the concentrations of viable microbes and immunotoxicological activity of the furniture dust. However, the method does not destroy or remove all fungal material present in the dust, as detected with QPCR analysis, and in some cases the cleaning procedure may increase the microbial concentrations and immunotoxicity of the dust (Huttunen et al., 2010; Klánová and Lajčíková, 2006). Certain resistance to the fungal colonization, even under very moist conditions, is attained to building materials with any lime composition or oily coating used (Piecková et al., 2007). Given the scientific evidence of mortality, morbidity, and subclinical effects of IAQ including dampness and mould, doctors should be proactive in the community and in their country as advocates for a healthier children environment (Moshammer et al., 2006).

A study performed by Singer et al. (2012) highlighted the contrast in different housing risk factors, i.e. noise and indoor pollution from cooking. For this purpose, the performance metrics of airflow, noise, and combustion product capture efficiency were measured for a sample of 15 cooking exhaust devices, as installed in residences. This study demonstrated that airflows of installed devices are often below advertised values and that less than half of the pollutants emitted by gas cooking burners are removed under several types of operational conditions. The most important finding is that for many commercial devices, achieving capture efficiencies that approach or exceed 75% requires operation at settings that produce prohibitive noise levels.

Meijer et al. (2006) assessed the influence of the location of a Dutch reference dwelling, integrating risks from multiple stressors related to houses close to traffic roads, taking into account noise and noise-related health outcomes (communication and sleep disturbance), particulate matter (PM_{10}), sulphur dioxide, benzene, and benzo[a]pyrene. Overall, the assessment due to the combined exposure to these types of stressors revealed that 90% of the related human health damage is attributable to noise; human health damage due to respiratory effects of PM_{10} accounts for about

5%, while the rest of the risks (including cancer due to benzene and benzo[a]pyrene) accounts for the remaining 5%. This study concluded that the human health damage due to combined traffic stressor exposure may be 1.5 to 2 times higher than the health damage associated with the rest of the dwelling life cycle (e.g. damage to human health due to exposure to substances emitted by building materials). Indoor noise has been found to be a major component of sleep disturbance, which is mostly related to either poor insulation or proximity to heavily trafficked streets. The likelihood of home accidents is significantly greater when the individual is tired all the time or most of the time;also there is an association between sleep disturbance and accidents, with 22% of those reporting an accident also reporting having their sleep disturbed during the previous four weeks (WHO Regional Office for Europe, 2009b). Moreover, noise related sleep disturbance is highly associated with domestic accidents (OR = 1.6, CI 1.4–1.9) as reported by the LARES survey (WHO Regional Office for Europe, 2007).

The LARES Survey (WHO Regional Office for Europe, 2007), coordinated by the WHO European Centre for Environment and Health, aimed at providing a broad overview of the effects of housing conditions on health status in eight European cities. In order to obtain statistically significant results, about 800 or more dwellings were selected in each city, resulting in a database covering more than 3000 dwellings and 8000 residents. The associations were based on the results of a detailed household questionnaire and an inspection form filled by the survey team, as well as an individual health questionnaire filled in by each occupant. Although the survey did not include quantitative assessment of IAQ or other health stressors and risk factors, several adverse health effects (such as hypertension, asthma, frequent migraine) were quantitatively associated with a variety of risk factors (e.g. sleep disturbed by noise), expressed by ORs. Potential synergistic effects among risk factors were not investigated in detail; yet, the LARES findings provide a wide overview for a variety of real life housing conditions.[6] In addition, risk factors of high impact (e.g. sanitary installations, accessibility, safety issues) were described in detail; this is of great importance due totraditional risk assessment being too focused on chemicals, which is often misleading considering the acute and detrimental effects of e.g. domestic accidents. An additional important outcome from the overall study is that insufficient housing conditions are strongly correlated to low SES, which affects most housing risk factors.

The WHO European Centre for Environment and Health recently prepared a guidance report detailing methods to estimate the disease burden caused by inadequate housing conditions (WHO Regional Office for Europe, 2011). This cross-European assessment of several individual housing risk factors demonstrates the applicability of the environmental burden of disease (EBD) methodology for housing-related health impact assessment.

The study did not cover all potential health risks from indoor exposure to chemicals (e.g. exposure to emerging compounds such as phthalates and risk of endocrine disruption); in addition, several risk parameters contributing to the same health outcomes (e.g. radon and secondhand smoke) were treated independently. This introduces large uncertainties on actual risk estimations and, consequently, to the estimated health impacts, especially considering that in real life—although not adequately described— people are exposed to multiple risk factors simultaneously. In addition, when dealing with a single risk factor, it is impossible to evaluate the overall impact of interventions, such as better insulation for improving building energy efficiency; similar interventions will result in better thermal conditions, however, the lower ventilation will contribute to elevated concentrations of pollutants emitted mainly indoors (e.g. household chemicals or building materials). Despite these limitations, the study covered a wide range of actual real life risk factors related to housing beyond traditional risk assessment (in a way similar to LARES), presenting the results of EBD using Disability-

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[6] In the context of a workshop on multiple exposure in indoor built environments, the WHO European Centre for Environment and Health has compiled some information on multiple exposure in European homes based on the LARES database. The findings have been portrayed in the introduction section of this report under "international data", but have not been published elsewhere.

Adjusted Life Years (DALYs) as a common final outcome and, allowing the direct interpretation of the relative importance of these different risk factors. The latter is very important for risk communication purposes and, eventually, risk management. Among the several risk factors, SHS was found to be the most detrimental one, associated to a mortality rate of 7.3 per 100 000 (i.e. mortality risk of $7.3 \cdot 10^{-5}$) exposed residents and an overall amount (including all related health endpoints) of 713 000 DALYs per year. A summary of the quantitative estimates of EBD is given below in Table 5.

Table 5. Summary of EBD calculations (adapted from WHO Regional Office for Europe, 2011)

Stressor	Health outcome	Environmental Burden From Housing per year (total and per 100 000 population)
Mould	Asthma deaths and DALYs in Children (0-14 years)	45 countries of WHO European Region: 83 deaths (0.06/100 000) 55 842 DALYs (40/100 000)
Dampness	Asthma deaths and DALYs in Children (0-14 years)	45 countries of WHO European Region: 103 deaths (0.07/100 000) 69 462 DALYs (50/100 000)
Lack of window guards	Injury deaths and DALYs (0-14 years)	WHO European Region: ~10 deaths (0.007/100 000) ~3310 DALYs (2.0/100 000)
Lack of smoke detectors	Injury deaths and DALYs (all ages)	WHO European Region: 7523 deaths (0.9/100 000) 197 565 DALYs (22.4/100 000)
Crowding	Tuberculosis	WHO Euro B and C subregions: 15 351 Tuberculosis cases (3.3/100 000) 3518 deaths (0.8/100 000) 81 210 DALYs (17.6/100 000)
Indoor cold	Excess winter mortality	11 European countries: 38 203 excess winter deaths (12.8/100 000)
Traffic noise	Ischaemic heart disease including myocardial infarction	Germany only: 3900 myocardial infracts (4.8/100 000) 24 700 ischaemic heart disease cases (30.1/100 000) 25 300 DALYs (30.8/100 000)
Radon	Lung cancer	Three western European countries: France: 1234 deaths (2.1/100 000) Germany: 1896 deaths (2.3/100 000) Switzerland: 231 deaths (3.2/100 000)
Residential Second Hand Smoke	Lower respiratory infections, asthma, heart disease and lung cancer	WHO European Region: 64 700 deaths (7.3/100 000) 713 000 DALYs (80.7/100 000)
Lead	Mental retardation, cardiovascular disease, behavioural problems	WHO European Region: 694 980 DALYs (79.2/100 000)
Indoor carbon monoxide	Headache, nausea, cardiovascular ischaemia/insufficiency, seizures, coma, loss of consciousness, death	WHO Euro A subregion: 114 – 1545 persons with DNS/PNS (0.03-0.4/100 000) 114 ± 97 deaths (0.03 ± 0.02/100 000)
Formaldehyde	Lower respiratory symptoms in children	WHO Euro A subregion: 0.3 to 0.6% of wheezing in children
Indoor solid fuel use	Chronic obstructive pulmonary disease (COPD), Acute lower respiratory infections (ALRI), Lung cancer	WHO European Region: 8490 ALRI deaths in children <5 (16.7/100 000) 293 600 ALRI DALYs in children <5 (577/100 000) 5800 COPD deaths in adults >30 (1.1/100 000) 100 700 COPD DALYs in adults >30 (19.3/100 000)

Physical and biological stressors and adverse indoor conditions

A recently published Cochrane collaboration review (Kendrick et al., 2012) looked into child injuries which, in industrialised countries, often represent the leading cause of childhood death. Furthermore, social gradients exist in child injury mortality and morbidity, with children living in disadvantaged circumstances being at greater risk of injury than those who are more advantaged. Most injuries in pre-schoolchildren occur at home, but there is little meta-analytic evidence that child home safety interventions effectively reduce injury rates or improve a safety practices. As well, there is little evidence whether the effects of such interventions vary by social group.

In the study, Kendrick et al. examined whether home safety education and providing safety equipment reduced injuries and increased safety behaviours and safety equipment use. It also looked at whether home safety education was more or less effective in disadvantaged families. The Cochrane Central Register of Controlled Trials, Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL, DARE, and ISI Web of Science, plus a range of relevant web sites, conference proceedings and bibliographies to May 2009 were searched in the frame of this study. These included: randomized controlled trials, non-randomized controlled trials and controlled before and after studies where home safety education with or without the provision of safety equipment was provided to young persons up to 19 years. The studies reviewed reported on safety practices, possession of safety equipment, and injury occurrence.

98 studies were included; 54 of which were included in at least one meta-analysis. 35 (65%) were randomized controlled trials and 19 (35%) included in the meta-analysis provided individual participant level data. There was a lack of evidence that home safety interventions reduced rates of thermal injuries or poisoning. There was some evidence that interventions may reduce injury rates after adjusting controlled before-after studies for baseline injury rates (pooled incidence rate ratio (IRR) 0.89, 95% CI 0.78 – 1.01). Greater reductions in injury rates were found for interventions delivered in the home (IRR 0.75, 95% CI 0.62 – 0.91), and for those interventions not providing safety equipment (IRR 0.78, 95% CI 0.66 – 0.92).

Home safety interventions were effective in increasing the proportion of families with safe hot tap water temperatures (OR 1.41, 95% CI 1.07 – 1.86), functional smoke alarms (OR 1.81, 95% CI 1.30 – 2.52), a fire escape plan (OR 2.01, 95% CI 1.45 – 2.77), storing medicines (OR 1.53, 95% CI 1.27 – 1.84) and cleaning products (OR 1.55, 95% CI 1.22 – 1.96) out of reach, having syrup of ipecac – a vomit-inducing medicine – (OR 3.34, 95% CI 1.50 – 7.44) or poison control centre numbers accessible (OR 3.30, 95% CI 1.70 – 6.39), having fitted stair gates (OR 1.61, 95% CI 1.19 – 2.17), and having socket covers on unused sockets (OR 2.69, 95% CI 1.46 – 4.96).

The above evidence reveals that physical injury and/or poisoning from accidental intake of smoke, chemicals, and pharmaceuticals inadequately stored in house are factors that may increase the overall risk of adverse health effects from indoor environmental exposure to chemical stressors and other indoor pollutants. There were no studies that studied the actual effect from combined exposure to these health stressors and risk modifiers. However, an obvious linkage can be drawn between inadequate protection from such hazards (e.g. child access to medicine and cleaning products, non-existence of functional smoke alarms, non-access to poison control centre numbers) and inadvertent environmental exposure to household chemicals, CO_2, CO, and PM, respectively. More targeted studies addressing the effective association of such safety hazards and indoor exposure to environmental health stressors are needed to establish a solid scientific basis for policy decision-making in this field.

For noise, a shift in research and practice (regulation) can be noticed from the time noise was treated only as a disturbance, to the recent realization that noise can have major health effects. Assessment of indoor environments under the wider perspective of comfortable living reveals that different needs are to be covered towards improving dwellings. Thus, most of the relevant noise studies are done as a part of studies evaluating multiple stressors and factors affecting housing

conditions, mostly driven by the recently increasing demand for more energy efficient buildings. A typical example is the assessment of passive houses in Denmark, including both quantitative measurements of these houses and qualitative interviews with the occupants about their experiences of the indoor environment (Brunsgaard et al., 2012), while an interactive top-down approach for a comprehensive management of the indoor environment is proposed in the Netherlands (Bluyssen, 2008). In terms of combined indoor exposure, Schulz et al. (2012), working on data from the fourth German Environmental Survey, studied subgroups with regard to (a) noise, hearing capacity and stress hormones, (b) chemical contamination of indoor air, and (c) biogenic indoor contamination. According to the first results of the study (Umweltbundesamt, 2008), 3% of the children 8 to 14 years of age were found to suffer initial hearing loss and approximately 14% showed a slight hearing impairment. According to their parents, 6% of the children felt disturbed by road traffic noise, and 5.5% by aircraft noise.

Prevalence of Sick Building Syndrome is enhanced by the combined action of exposure to biological agents and chemicals (Haverinen-Shaughnessy et al., 2007; Sahlberg et al., 2013), especially SHS (Hulin et al., 2012; Jedrychowski et al., 2007; Pirastu et al., 2009; Sahlberg et al., 2009) or additional parameters related to thermal conditions, safety, and satisfaction/discomfort (Turunen et al., 2009). The development of mould and dampness is greatly facilitated by specific house characteristics, such as temperature and relative humidity (Polizzi et al. 2012), as well as ventilation conditions (Burr et al., 2007; Frisk et al., 2007; Meyer et al., 2011; Piontek et al., 2011). Exposure to certain home conditions related to mould and dust in the first year of life increased the risk of allergic disease, whilewell insulated windows protected against allergic rhinoconjunctivitis and severe atopic eczema in the first year of life (Ibargoyen-Roteta et al., 2007). In addition, houses with reported water damage (Haverinen-Shaughnessy et al., 2006; Jaakkola et al., 2010; Polizzi et al., 2009) appear to be very susceptible to develop mould and dampness. The chemical composition in terms of organic fraction of the materials (plasters, finishes, and paints) is also a significant determinant on the growth rate of moulds (D'Orazio et al., 2009). Interior surface materials and recent renovations at home were also found to be a parameter related to mould and dampness and the risk of asthma (Jaakkola et al., 2006), while living room floor β (1 $\rightarrow$ 3)-glucan and fungal extracellular polysaccharides concentrations were largely determined by the type of floor sampled (Giovannangelo et al., 2007a).

The studies related to thermal conditions mostly focus on the adequacy of ventilation for achieving good levels of IAQ, in combination to adequate acoustic performance, and minimum energy consumption for achieving thermal comfort. A number of studies aim at optimizing house design to reach an acceptable level of IAQ and thermal comfort, as well as minimizing energy consumption and carbon footprint (Shahrestani et al., 2013). Limited studies also incorporate acoustic and visual comfort in a wider perspective of indoor dwellings and human well-being (Mlecnik et al. 2012; Sarbu and Sebarchievici, 2013). The need to improve the energy efficiency of buildings requires new and more efficient ventilation systems and innovative operating concepts that make use of natural ventilation seem to be more appreciated by occupants. Among the buoyancy-driven ventilation strategies that are currently available, single-sided natural ventilation has proved to be very effective and can provide high air exchange rates for temperature and IAQ control. Short-term window airing is very effective and can provide both acceptable IAQ and thermal comfort conditions in buildings (Heiselberg and Perino, 2010).

Crowding is a typical example of exposure to multiple risk as it is frequently associated with noise and inadequate hygiene standards and inversely related to SES (Evans et al., 2010). To account for the intrinsic nature of combined exposure when assessing crowding, Wachs and Evans (2009) introduced the concept of "chaotic households". Chaotic households are characterized by noise, crowding, and a lack of routine and order. Although households with more chaos are disproportionately likely to be socioeconomically disadvantaged, chaos is associated with poorer developmental outcomes for all children, regardless of SES (Deater-Deckard et al., 2009; Evans et al.,

2005; Hart et al., 2007). Specifically, children living in chaotic home environments have been found to exhibit poorer academic, socio-emotional, and self-regulatory outcomes. Studies have also demonstrated links between specific dimensions of chaos and young children's cognitive growth. For example, crowding in the home during infancy has been linked to poorer cognitive and communication skills (Evans et al., 2010).

A multicenter study of the epidemiology of allergic diseases in Poland, the Polish Multicentre Study of Epidemiology of Allergic Diseases (PMSEAD), was designed to study the prevalence and risk factors for asthma in Poland in thirty-three areas selected in 11 regions of Poland (Liebhart et al., 2007). Results were obtained for asthma in 16 238 subjects, including 3268 children (aged 3 to 16 years) and 12 970 adults (17 to 80 years). The overall prevalence of asthma was 8.6% (95% CI 7.7% – 9.6%) among children and 5.4% (95% CI 5.0% – 5.8%) among adults. Several risk factors for asthma were identified: family history of asthma, black smoke, residential exposure to traffic-related air pollution in children and adults, dampness, and overcrowded housing in adults. The study concluded that indoor risk factors appeared to be significant only in the adult sample. The most significant among them were living in damp houses (OR 1.53; 95% CI 1.29–1.81) or in overcrowded houses (OR 1.35; 95% CI 1.05–1.75). No statistically significant association was observed for passive smoking in the home, use of gas stoves, pet ownership, or exposure to ambient air pollution with sulfur dioxide.

Jackson et al. (2013) have reviewed seven risk factors for severe ALRI in children. Of these seven risk factors, crowding (defined as more than 7 people per household or more than 2 people sharing child's bedroom or more than 2 people per room) was found to be significantly associated with severe ALRI consistently across studies. Results of the meta-analysis provided an OR (with 95% CI) of 1.96 (1.53-2.52). Other risk factors showed the following OR values: low birth weight 3.18 (1.02-9.90), lack of exclusive breastfeeding 2.34 (1.42-3.88), exposure to indoor air pollution 1.57 (1.06-2.31), incomplete immunization 1.83 (1.32-2.52), undernutrition (defined as weight-for-age less than 2 standard deviations) 4.47 (2.10-9.49), and HIV infection 4.15 (2.57-9.74)

Finally, we need to recognize that there is significant change in the types of material used in furnishings over the last 50 years (Weschler, 2009). Veneer on composite-wood has replaced solid wood in many furnishings. It is common today for kitchen cabinets, dressers, bed frames, desks and similar products to be constructed primarily with medium density fiberboard or a similar composite wood material. The cushioning used in bedding, sofas and chairs has evolved from feathers and down to synthetic foams. Since the 1960s, most synthetic foams have been treated with flame-retardants. For example, polyurethane foam used in home cushioning often contains 10–30% (by weight) BFR. Building materials and furnishings may be loaded with contaminants, which are released slowly when indoors acting as effective chemical storage. According to Sterman and Hult (2013), some chemical classes commonly used in building materials, furnishings, and consumer products have been shown to be endocrine disrupting chemicals – they interfere with the action of endogenous hormones (Rudel and Perovich, 2009). These include PCB, used in electrical equipment, caulking, paints, and surface coatings; chlorinated and brominated FR, used in electronics, furniture, and textiles; pesticides, used to control insects, weeds, and other pests in agriculture, lawn maintenance and the built environment; phthalates, used in vinyl, plastics, fragrances and other products; alkylphenols, used in detergents, pesticide formulations and polystyrene plastics; and parabens, used to preserve products like lotions and sunscreens.

Overall, the actual exposure to compounds emitted by building products is the result of the combination of multiple parameters, starting from the manufacturing processes (that define the compounds potentially emitted by the material), the parameters affecting emissions from the material (e.g. indoor temperature and humidity), and the parameters affecting indoor concentration, such as extent of product use, dwelling ventilation and residential behaviour. All this interactions (starting from the initial stage of the life cycle of a building product) are graphically illustrated in Fig. 8 (Salthammer and Bahadir, 2009).
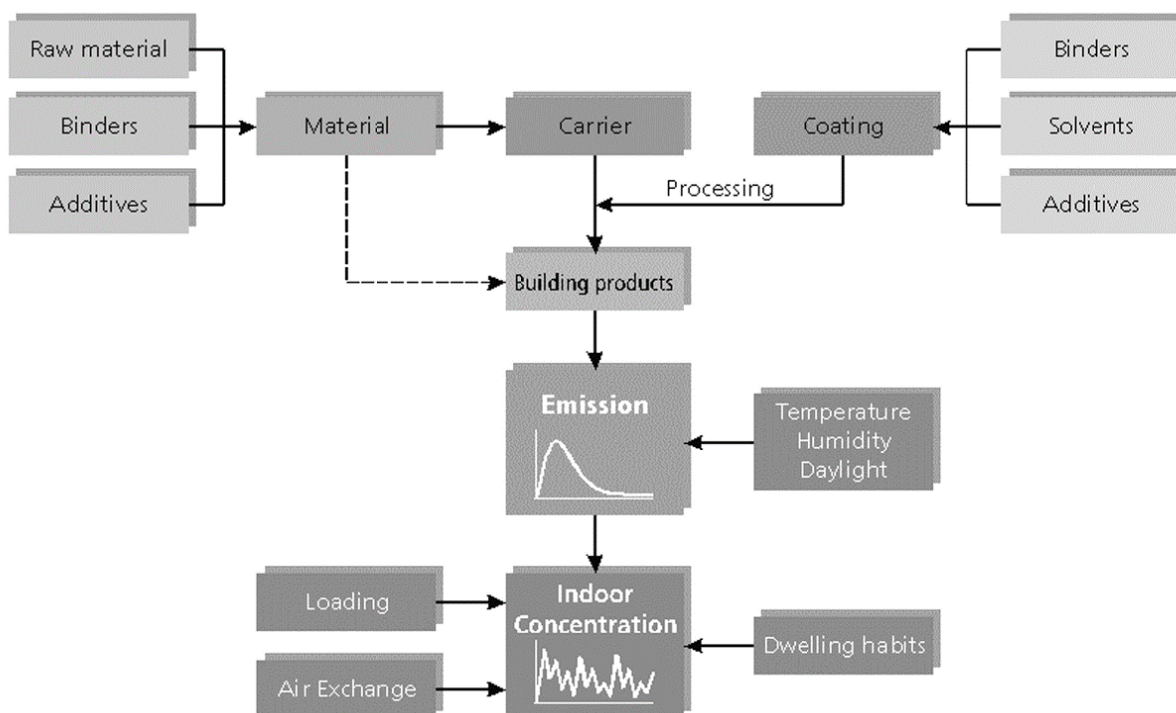
Fig. 8. Influence of applied materials, processing, climatic parameters and living behavior on emissions from a building product and indoor concentrations (Salthammer and Bahadir, 2009).

Schools/Kindergartens

Chemical mixtures/indoor pollutants

The cross-sectional EU-funded HESE (Health Effects of School Environment) study explored the effects of IAQ on respiratory health of schoolchildren living in Norway, Sweden, Denmark, France and Italy (Simoni et al., 2010). Particulate matter with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10}) and CO_2 levels in a day of normal activity (full classroom) were related to wheezing, dry cough at night, and rhinitis in 654 children (10 yrs) and to acoustic rhinometry in 193 children. Schoolchildren exposed to PM_{10} >50 μg/m^3 and CO_2 >1,000 ppm (standards for good IAQ) were 78% and 66%, respectively. All disorders were more prevalent in children from poorly ventilated classrooms. Schoolchildren exposed to CO_2 levels >1,000 ppm showed a significantly higher risk for dry cough (OR 2.99, 95% CI 1.65-5.44) and rhinitis (OR 2.07, 95% CI 1.14-3.73). By two-level (child, classroom) hierarchical analyses, CO_2 was significantly associated with dry cough (OR 1.06, 95% CI 1.00-1.13 per 100 ppm increment) and rhinitis (OR 1.06, 95% CI 1.00-1.11). Nasal patency was significantly lower in schoolchildren exposed to PM_{10} >50 μg/m^3 than in those exposed to lower levels.

In Stockholm (Sweden) the effect of air exchange rate and the presence of human activity on $PM_{2.5}$, soot, and NO_2 were measured (Wichmann et al., 2010) during winter and summer indoors and outdoors at six schools. Indoor environments were free of SHS and gas appliances, as the aim was to assess to what extent $PM_{2.5}$, soot and NO_2 infiltrate from outdoors to indoors. The median indoor and outdoor $PM_{2.5}$ levels were 8.3 μg/m^3 and 8.6 μg/m^3, respectively and the median indoor/outdoor ratio was 0.89. In the same city, fine particles ($PM_{2.5}$) were sampled indoors in ten classrooms in five schools, in three communities, during nine 2-week periods (Molnár et al., 2007). Each sampling site was sampled twice, once during winter and once during spring. The samples were

68

analysed for elemental concentrations using X-ray fluorescence spectroscopy. In all locations significantly higher outdoor concentrations were found for elements that are related to long-range transported air masses (sulfur, nickel, bromine, and lead), while only titanium was higher indoors in all locations. Similar differences for sulfur, bromine, and lead were found in both seasons. In pre-schools different seasonal patterns were seen for the long-range transported elements sulfur, bromine, and lead and the crustal elements titanium, manganese, and iron. The indoor/outdoor ratios for sulfur and lead suggest an outdoor $PM_{2.5}$ particle net infiltration of about 0.6 in these buildings. The community located 25 km from the city centre had significantly lower outdoor concentrations of elements of crustal or traffic origin compared with the two central communities, but had similar levels of long-range transported elements. Significant correlations were identifiedbetween $PM_{2.5}$ and most elements outdoors (rs = 0.45-0.90). Copper levels were found to correlate well (rs = 0.64-0.91) with the traffic marker NO_2 during both winter and spring in all locations.

A study conducted in Germany explored the exposure of children to indoor air pollutants in German schools by analysing data on air quality in 92 classrooms in winter (2004/2005) and 75 classrooms in spring/summer (2005) in 64 schools (Fromme et al., 2006). To assess IAQ, CO_2, PM, and VOC were monitored on a school day in each classroom. Real-time measurements of particle mass (PM_1, $PM_{2.5}$, PM_4, PM_{10}) were done using an optical laser aerosol spectrometer. Additionally, for each classroom descriptive data on size, number of subjects in the classroom (including the teacher), and occupancy periods were collected by a standardized form. The median PM_{10} and $PM_{2.5}$ in a classroom ranged from 16.3 to 313 $\mu g/m^3$ and 2.7 to 81 $\mu g/m^3$, respectively, during the winter period, whereas the PM fraction concentration in summer varied from 18.3 to 178 $\mu g/m^3$ (PM_{10}) and 4.6 to 34.8 $\mu g/m^3$ ($PM_{2.5}$), respectively. PM concentrations in the summer were significantly lower than in the winter.

Literature data on indoor concentrations in schools and kindergartens are often deficient in geographical resolution and chemical speciation. The work of Sarigiannis et al. (2011) has been taken as the basis for this analysis as it brings together literature data covering twenty years of work. The review, however, reports concentration data in schools/kindergartens only for few VOC and carbonyls. As an example of a southern European location pollution levels, Greek schools/kindergartens show an average value of 5.33 $\mu g/m^3$ (3.1 $\mu g/m^3$ – 7.8 $\mu g/m^3$) of benzene and 16.55 $\mu g/m^3$ (13.8 $\mu g/m^3$ – 20.2 $\mu g/m^3$) of formaldehyde. These results are in good agreement with the data reported by Missia et al. (2009) who measured an average concentration of 5.5 $\mu g/m^3$ of benzene and 12.95 $\mu g/m^3$ (4.9 $\mu g/m^3$ – 21 $\mu g/m^3$) of formaldehyde in three different schools in Greece. The same chemical compounds account for average values in Dutch schools/kindergartens of 1.42 $\mu g/m^3$ (0.8 $\mu g/m^3$ – 3.0 $\mu g/m^3$) of benzene and 13.93 $\mu g/m^3$ (6.1 $\mu g/m^3$ – 22.4 $\mu g/m^3$) of formaldehyde. Concentrations levels of other chemicals are not reported.

The work of Stranger et al. (2007) provided more data regarding indoor concentrations of BTEX as well as $PM_{2.5}$ and NO_2 in 27 schools in Antwerp (Belgium). Results reveal multiple exposure to the above pollutants with average concentrations of 0.98 $\mu g/m^3$ for benzene, 4.44 $\mu g/m^3$ for toluene, 3.52 $\mu g/m^3$ for xylene, 1.07 $\mu g/m^3$ for Ethylbenzene, 61 $\mu g/m^3$ (11.0 $\mu g/m^3$ – 166 $\mu g/m^3$) for $PM_{2.5}$, and 57 $\mu g/m^3$ (14 $\mu g/m^3$ -159 $\mu g/m^3$) for NO_2. Indoor benzene in schools appeared to be the main BTEX component. Its occurrence was linearly correlated with the local outdoor concentrations suggesting that infiltration from outdoor air is the main source of indoor pollution. No linear correlations could be established between the indoor and outdoor concentrations of toluene, ethylbenzene, and the xylene isomers. Furthermore, the indoor microenvironment indicated levels of ethylbenzene and the three xylene isomers that were strongly linearly correlated to each other (R = 0.851–0.966, 99% significance level) indicating the presence of common sources and, consequently, the high probability to have combined exposure to these three VOC. Analysis of the data on the basis of the location of the schools shows that BTEX concentrations are always higher in the schools located in the suburban part of the city than the one located in the urban environment. This is particularly evident for benzene where concentrations in urban schools are on the average

more than three times higher than the ones measured in suburban schools. A comparison with the typical values of BTEX found in residential dwellings shows that concentration of BTEX are generally lower in schools/kindergartens than in residential dwellings; this is attributable to the lack of combustion sources which are normally present in residential dwellings. Concentrations of formaldehyde are also lower in schools/kindergartens than in homes, but in this case the difference is lower than for BTEX showing that common sources of emission, such as construction products and furniture, are present in both indoor setting types.

In Kozani (Greece) during the winter period of 2008, a study on indoor air pollution was carried out in three schools (Missia et al., 2009). The buildings were selected according to the following criteria: (a) age (less than two years); (b) the last reconstruction or renovation; (c) position of the building (urban sites preferred); and (d) building availability. The concentrations of the majority of measured substances were in general below and only in some cases higher than 10 $\mu g/m^3$. High VOC indoor concentrations could be explained by low ventilation rates in the tested sites. Concerning the high indoor concentrations of formaldehyde, acetone, and benzene, it is clear that these values indicate relatively significant emission sources in all buildings. High indoor concentrations of benzene could be associated with the presence of central heating systems inside the building and the fact that refilling of the tank with heating diesel was carried out during the sampling period. Finally, the construction product emissions, with regard to formaldehyde, in the two schools originated to a large extent from furniture.

A study carried out in France analysed relationships between IAQ in schools and the allergic and respiratory health of schoolchildren (Annesi-Maesano et al., 2012). A survey was conducted in a large sample of classrooms of primary schools in France to provide objective assessments of IAQ in classrooms and to relate exposure to major air pollutants to asthma and allergies of schoolchildren. A significant positive correlation was found between exercise-induced asthma and the levels of $PM_{2.5}$ and acrolein in the same week.

Chemical, biological, and physical stressors

A key study dealing with multiple exposure in schools was carried out by Pénard-Morand et al. (2010) where the impact of urban air pollution, assessed through reliable indicators of exposure, on asthma and allergies in schoolchildren was evaluated. A total of 9,615 children (mean age 10.4 yrs) were recruited to participate in the French Six Cities Study, which was intended to estimate the prevalence and the severity of asthma and allergies and to identify the associated risk factors. The sample was taken from all pupils in the 401 relevant classes from 108 schools randomly selected in the six French communities (Bordeaux, Clermont-Ferrand, Creteil, Marseille, Strasbourg and Reims), which were chosen due to their variability in air quality. Long-term exposure of the 6,683 children for whom complete health data were available was assessed through 3-year averaged (from 1998 to 2000) concentrations of major urban air pollutants (benzene, VOC, SO_2, PM_{10}, NO_2, NO_x and CO), estimated at the 108 school addresses. From the study, it was found that associations of (a) lifetime asthma with benzene, SO_2, and PM_{10}, and (b) sensitization to pollens with PM_{10} were particularly robust. Restricting the analyses to the 2,213 children who have resided in their current home since birth yielded ORs similar to those obtained for the 2,834 8-year resident children. In spite of the reduction of the sample size, the associations of lifetime asthma with benzene (OR 1.3, CI 1.0–1.9; p=0.04) and PM_{10} (OR 1.4, CI 1.0–2.0; p=0.05) remained significant. Moreover, of borderline significance were the associations of sensitization to pollens with VOC (OR 1.3, CI 1.0–1.9; p=0.07) and PM_{10} (OR 1.2, CI 1.0–1.9; p=0.10). Although the study did not include actual indoor measurements, modelled outdoor concentrations were used as a reliable proxy of indoor concentrations due to the close proximity of schools to traffic.

Wallner et al. (2012) studied air pollution in schools in Austria and its effect on lung function. In a cross-sectional approach, differences in indoor pollution in nine elementary all-day schools were assessed and 34 of these pollutants were analysed for a relationship with respiratory health

determined by spirometry and using a linear regression model. Indoor climate factors (temperature, humidity) as well as chemical factors were measured. The 252 chemical indoor air parameters comprised of the following substance groups (number of compounds in brackets): alcohols (2), chlorinated hydrocarbons (4), aromatic hydrocarbons (12), aliphatic hydrocarbons (13), terpenes (3), aldehydes (9), other relevant compounds including NO_2 (10), volatile compounds in PM/school dust (26), musks (5), phenols (19), phthalates (11), trisphophates (9), PAH (16), PCB (7), organophosphorous esters (7), organochlorine pesticides (22), other pesticides (3), polybrominated diphenyl ethers (20), organotins (6), metals (19), pyrethroids (12), inorganic components (8), industrial chemicals (3), disinfectants (1), caffeine and nicotine (2), and total elemental and organic carbon (3). A negative association was found between air flow in the lungs of schoolchildren and formaldehyde in the air, benzylbutylphthalate and the sum of polybrominated diphenylethers in school dust. Moreover, ethylbenzene, m-, p-xylene and o-xylene revealed significant negative correlations with FVC (forced vital capacity) and FEV1 (forced expiratory volume in the first second). Overall, these results suggest that indoor air pollutants, though found at relatively low concentrations in elementary schools, may adversely affect the lung function of children.

A wide variety of IAQ parameters including PM_{10}, $PM_{2.5}$, VOC, NO_2, O_3, airborne/deposited moulds, CO_2 and thermal comfort (measurements of temperature and relative humidity) were evaluated in a study conducted in primary school classroom in Beusichem (Netherlands) during periods of two weeks in February and June 2010 (Scheepers et al., 2012). Beyond the assessment of classroom IAQ, the study aimed at the evaluation of the performance of portable air treatment units (PATUs). Sampling was carried out in occupied and non-occupied classrooms. Indoor PM_{10} concentrations were elevated inside the occupied classroom (86 and 102 $\mu g/m^3$ for winter and summer, respectively), while during the use of PATUs a small increase was observed in winter and a significant drop in the summer (91 and 60 $\mu g/m^3$, respectively). Formaldehyde levels were higher in summer (23 $\mu g/m^3$) than in the winter (15 $\mu g/m^3$), the same trend occured for TVOC (504 versus 305 $\mu g/m^3$). All of these compounds are stronglyassociated with health outcomes such as lifetime asthma (PM and formaldehyde, see Annesi-Maesano et al. 2012), rhinitis (TVOC, see Billionnet et al. 2011) and lower respiratory symptoms (formaldehyde, see WHO 2011), thus combined exposure to these types of compounds at these levels is expected to pose significant risks for children health. In terms of capability of PATUs to improve classroom air quality, it was concluded that removal efficiency of air pollutants is reversely correlated to classroom occupancy.

Another study done In Ankara (Turkey) investigated indoor and outdoor air quality in a primary school, a kindergarten, and an office (Mentese et al., 2009). Indoor air pollutants, bioaerosols (bacteria and airborne fungi), VOC, and $PM_{2.5}$ were measured for five consecutive days in each site both in the summer and in the winter season. Indoor VOC and bioaerosol levels were found to be higher in primary school and kindergarten than in the workplace.

In Athens, (Greece), the concentration levels of PM, airborne fungi, CO_2 as well as temperature and relative humidity were investigated in the indoor and outdoor environment of two schools during the period January to May 2011 (Dorizas et al., 2013). The overall concentration ranges of the indoor measured pollutants were: PM_{10}: 14.92-166.18 $\mu g/m^3$, $PM_{2.5}$: 3.16-31.27 $\mu g/m^3$, PM_1: 0.72-9.01 $\mu g/m^3$, UFP: 4188- 63093 pt/cm^3, total airborne fungi: 28-2098 CFU/m^3 and CO_2: 389-1717 ppm.

Another interesting study was carried out by Pegas et al. (2012b) in Aveiro (Portugal), where multiple pollutant concentrations inside and outside school buildings at different locations (city centre and suburban) were investigated between April and June 2010. The aim was to simultaneously evaluate comfort parameters (temperature, relative humidity, CO_2 and CO) and indoor and outdoor concentrations of VOC, NO_2, PM_{10} and bioaerosols. PM_{10} samples were analysed and characterized for the water soluble inorganic ions, organic carbon, elemental carbon, carbonates, and detailed organic speciation. The average PM_{10} concentration was 49.2/13.0 and 72.8/20.4 $\mu g/m^3$ during weekdays/weekends for the schools allocated in city centre and suburbs

respectively. The daily indoor PM_{10} levels were always higher than those outdoors, except on weekends, suggesting that the physical activity of pupils and class works highly contributed to the emission and re-suspension of particles. Higher PM_{10} concentrations at the suburban school are explained by the proximity to industrial emissions. A strong correlation of the CO_2 level with occupancy has been observed. During the occupation period, in the city centre school, the CO_2 levels ranged widely from 899 to 2540 mg/m^3, while in the suburban school, values were between 833 and 1859 mg/m^3. Comparable NO_2 concentrations were obtained in both schools. Levels were below the annual and hourly limit values (lower thresholds) of 26 mg/m^3 and 100 mg/m^3, respectively, for the protection of human health, stipulated by the Air Quality Directive 2008/50/EC. The total bacterial colony-forming units in both indoor and outdoor air were above the acceptable maximum value of 500 CFU/m^3. At all locations, the indoor concentrations of atmospheric aldehydes (formaldehyde, acetaldehyde, propionaldehyde, and benzaldehyde) were higher than those outdoors, particularly for formaldehyde. Formaldehyde concentrations ranged from 1.48 to 42.3 $\mu g/m^3$. Higher levels in classrooms than outdoors suggest that indoor sources are more important contributors to the indoor levels than outdoor sources such as infiltration of vehicle exhaust (Ongwandee et al., 2009). Concentrations of formaldehyde are significantly affected by building age: i levels were higher in the presence of furniture bought new or restored less than one year before measurements, confirming the findings of Lovreglio et al. (2009). In general, concentrations of VOC were higher indoors than outdoors for both schools. Similarly to carbonyl compounds, inadequate ventilation observed lead to accumulation of pollutants emitted from specific indoor sources.

Physical and biological stressors and adverse indoor conditions

With regard to school indoor environments, reduction of exposure to noise is in contradiction to sufficient ventilation in class rooms (Mumovic et al., 2009). Considering that the main source of ventilation in the majority of schools is window opening, the occupants of the classroom (i.e. pupils and teachers) in noisy areas tend to shut windows especially during quiet activities (i.e. silent and lecturing activities) to reduce the distracting effect of external noise (Montazami et al., 2012). This results in an increased likelihood of classrooms experiencing overheating in hot weather and poor air quality due to the lack of sufficient ventilation. Considering the contradicting needs for sufficient IAQ, lighting, thermal comfort, and acoustic performance, a study carried out in the Lisbon area (Portugal) highlighted that CO_2 concentrations found in five classrooms of three schools were higher than those recommended by the Portuguese legislation and all the values for sound pressure level were above the WHO recommendations (Viegas et al., 2009).

A number of studies have focused on improving indoor environments at schools, considering that working or studying in a comfortable environment enhances not only well-being, but also satisfaction and, therefore, productivity and learning (Zeiler and Boxem, 2009). Assessment of thermal comfort in combination to IAQ is carried out by a combination of perception descriptive measures (by response to questionnaires) and field measurements (De Giuli et al., 2012). Common problems reported are high CO_2 concentration levels, which confirm insufficient air exchange by means of open windows, occasional insufficient lighting levels over the desks and, in general, non-uniform illuminance-distribution, probably due to improper solar shading use or even inappropriate shades. Pupils mostly complained about thermal conditions in warm seasons, poor IAQ, and noise. Classroom conditions also depended strongly on teachers' preferences. More detailed monitoring of IAQ revealed that higher coarse particle fraction concentrations are observed at higher indoor air temperatures and CO_2 concentrations (Polednik, 2011), highlighting that concentrations of small particle fractions are positively correlated with indoor air relative humidity. Crowding is also found to be a determinant of IAQ and thermal comfort, since in Portuguese high school buildings poor IAQ and thermal comfort was associated with high density of students in class rooms (Dias et al., 2011), while during summertime, IAQ and thermal comfort require maximum natural ventilation by opening both windows and doors (Conceição et al., 2008). However, climatic differences across Europe affect the way IAQ, thermal and acoustic performance are dealt with. Studies in England

have found that classrooms are often inadequately ventilated, resulting in increased risk of negative impacts on the pupils (Mumovic et al., 2009), however, the study showed that it was possible to achieve natural ventilation designs that met the criteria for indoor ambient noise levels when external noise levels were not excessive. Similarly to Portugal, natural ventilation by the given window areas was just sufficient to provide the minimum of 3 l/s^{-1} per person at low and intermittent occupancy, showing that overcrowding of classes might overwhelm the building design specifications for sufficient IAQ and thermal comfort.

A study in Frankfurt, Germany (Heudorf, 2008) was conducted in winter 2007 in two classrooms of a passive house school. Data on PM_{10} in the indoor air of classrooms, before and after intensified cleaning, are reported. In parallel, a documentation of the number of persons present in the room, their activity, and ventilation was done according to a standardized protocol. Measurements were collected for a period of three weeks. During the first week, the normal school situation was analysed, i.e., the classrooms were ventilated as usual and were cleaned by wet wiping twice a week. During the second and third weeks, the rooms were cleaned every day, so that the effect of intensified cleaning could be studied. Results showed that during the first week the mean particulate concentration was 86 $\mu g/m^3$ (median 60 $\mu g/m^3$), while during the 2nd and 3rd weeks mean concentrations decrease to 60 $\mu g/m^3$ (median 53 $\mu g/m^3$). Although an impact of cleaning on levels of indoor particles could be established, indoor PM_{10} levels were dominated by indoor factors, such as occupancy and activity of the persons in the room. However, after subtraction of the outdoor PM_{10} levels from the indoor levels, the "indoor part" was approximately 50 $\mu g/m^3$ during the first week, and approximately 30 $\mu g/m^3$ during intensified cleaning. Further detailed investigations showed the predominance of particles >1 μm indoors, which could easily be diminished by cleaning and ventilation. Indoor particles <0.5 μm, however, were increased via ventilation. The author concluded that higher levels of PM in the indoor air of classrooms have to be considered as an indicator of low hygiene and of increased and avoidable health risk for pupils and teachers. The data indicated the relevance of cleaning – and with regard to PM <1 μm also of ventilation – for the reduction of PM in classrooms.

Day care centers

Chemical mixtures/indoor pollutants

In Stockholm (Sweden) the effect of air exchange rate and the presence of human activity on $PM_{2.5}$, soot, and NO_2 were measured by Wichmann et al. (2010) indoors and outdoors at 10 pre-schools during winter and summer, aiming at the assessment of outdoors pollution contribution to indoors. The median indoor and outdoor $PM_{2.5}$ levels were 5.9 $\mu g/m^3$ and 6.1 $\mu g/m^3$, respectively and the median indoor/outdoor ratio was 0.95. Their infiltration factors were influenced by the micro-environment, ventilation type and air exchange rate, concluding that indoor environments occupied by children offer little protection against outdoor combustion-related particles and gases.

Chemical, biological and physical stressors

Day care centers are occupied by infants and kids aged below five years old, who are characterized by increased susceptibility to chemical and biological stressors. Nevertheless, the scientific evidence for IAQ in day care facilities is limited. The most comprehensive study was carried out by Roda et al. (2011). IAQ of 28 day care centers in Paris was investigated for biological contaminants (dust mite allergens, endotoxins, airborne fungi), chemical pollutants including aldehydes, VOC, and NO_2, as well as temperature and relative humidity. The results indicated that for all VOC except benzene, indoor concentrations were higher to the respective outdoor levels, a fact related to the existence of VOC-emitting materials and activities including painting and the necessary hygienic cleaning schedule. However, due to the better ventilation required by law in day-care centers, these levels

were lower to the ones measured in homes. Similarly, aldehydes concentrations in day care centers were lower than in dwellings, suggesting fewer sources and presence of older materials; still, formaldehyde concentrations ranged from 4.8 up to 40.1 $\mu g/m^3$, a fact that raises some concern regarding the well-known association of formaldehyde with lifetime asthma, enhanced by the susceptibility of the exposed population (very young children). NO_2 levels, although lower to the outdoor ones, were higher compared to Paris homes, mainly due to the proximity to trafficked roads and increased ventilation. Finally, biological contamination was higher than the values at home and could be explained by the penetration of outdoor contamination. Increased levels of endotoxins were identified as well and might be a consequence of high occupancy levels and frequent diaper changes. An interesting aspect with regards to day-care centers is the presence of PVC floors characterized by phthalates emissions (Xu et al., 2010), which in turn are well known endocrine disruptors (Latini et al., 2004). Considering the elevated exposure of infants and toddlers to phthalates through multiple pathways and especially non-dietary ingestion through settled dust (Beko et al., 2013), exposure to phthalates, although not measured, is expected to be significant. This is also confirmed by other relevant studies in Palermo, Italy (Orecchio et al., 2013) and Stockholm, Sweden (Bergh et al., 2011).

The fact that natural ventilation in crowded indoor settings is not always adequate for sufficient indoor quality was shown in the case of Latvian day care centers (Stankevica, 2011). Although thermal comfort was sufficient, carbon dioxide concentrations exceeded 1000 ppm in 75% of the day care centers studied, with the highest concentration level (1356 ppm) measured in a renovated facility with a natural ventilation system. The author thus recommended the installation of a more efficient ventilation system (mechanical), since opening of windows itself could not provide the optimal conditions indoors.

Annex 3: Health relevance of indoor pollutants

The ENVIE project (Carrer et al., 2008) reviewed the main important projects on indoor air related health effects. Based on this evidence the following diseases have been prioritized as being caused or aggravated by poor IAQ: allergic and asthma symptoms; lung cancer; COPD; airborne respiratory infections; cardiovascular mortality and morbidity; and odor and irritation (SBS symptoms).

Allergic and asthma symptoms

According to the ENVIE project, different types of key exposure agents of the indoor environment may have a role in development of allergy and asthma, including microbial, physical and chemical agents.

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

Chemicals – Chemicals that may play an important role in triggering asthma symptoms include: formaldehyde, aromatic and aliphatic chemical compounds, phthalates or plastic materials and indoor chemistry products resulting from ozonolysis of terpenes may also play a role, but the evidence is more limited (ECA, 2007).

Particles – SHS and indoor ultrafine particulate matter may trigger asthma symptoms (Strachan, 2000). Other triggering factors might be, wood or oil smoke, soot, or exhaust.

Indoor allergen exposure is recognized as being the most important risk factor for asthma in children, especially in terms of sensitization during the first years of life. The indoor environment in general can give symptoms of a non-specific nature, which is called 'sick-building syndrome'. According to the ENVIE project (Carrer et al., 2008), dwellings and schools frequently have severe indoor problems because of poor building construction and maintenance, poor cleaning and poor ventilation; accordingly, high levels of VOC, allergens, and mould (indicating humidity issues) have often been found.

Policy options

The following measures seem to be effective based on the reviewed literature:

- prevention of indoor smoking;
- prevention of moisture/mould growth in the building;
- prevention of allergen sources;
- adequate cleaning and maintenance with less harmful products, practical shaping of the interior to facilitate cleaning and maintenance;
- good control of the maintenance of heating and ventilation to ensure a satisfactory temperature and ventilation in the classroom;
- adequate periodical monitoring of the IAQ parameters;
- appropriate training of students, teachers, and school staff who are responsible for management, maintenance, and cleaning.

Lung cancer

Available data in the literature indicate the role of the following indoor pollutants:

Radon – Radon is considered to be the second cause of lung cancer. From the pooling of 13 residential radon epidemiological studies in 9 EU countries it has been estimated that about 9% of lung cancer deaths may be due to radon exposure in the home (McLaughlin and Bochicchio 2007).

Indoor pollutants

Second-Hand Smoke (SHS) – SHS has been classified as a Group 1 carcinogen by the International Agency for Research on Cancer. Studies conducted in the '90s have elucidated the relationship between exposure to SHS and lung cancer and relative risks (RR) have been provided, resulting in 1.36 for men and 1.22 for women. A recent study (Quantitative Estimation of Lung Cancer Deaths Attributable to Passive Smoking Exposure in Europe) indicated a total of 916 (54-1928) lung cancer cases due to exposure from a smoking spouse for males and 2,449 (1,424-3,357) for females. These figures correspond to an attributable proportion of 0.5% in males and 4.6% in females (Boffetta et al., 1998; Hackshaw et al., 1997). The largest burden of attributable cases derive from Western and southern Europe (Porta et al., 2007).

Combustion particles –The initial suggestion that lung cancer incidence increases due to long term low-level exposure to PM was provided by the Harvard Six Cities study (Dockery et al., 1993). These findings were confirmed in the long-term follow-up of the American Cancer Society, consisting of around 500 000 adults from metropolitan areas throughout the USA. Results indicated that each 10 $\mu g/m^3$ elevation in $PM_{2.5}$ was associated with approximately a 14% increase in lung cancer mortality. Evidence is emerging that long-term exposure to low concentration of PM is also associated with all-cause mortality.

European studies of PM exposure and lung cancer do not show a clear association, but uncertainties remain for the measurement of exposure and latency (Gallus et al., 2008).The main problem affecting these studies is represented by exposure assessment and its consequent role in cancer development. The presence of a latency period after exposure in the onset of cancer also represents an element to be accounted for in the study design. Further observations are hence required to corroborate the hypothesis of an increased risk of lung cancer.

Epidemiological studies conducted in mainland China, Taiwan and Singapore have consistently demonstrated that exposure to cooking oil fumes, particularly in the absence of fume extractors, is significantly associated with an increased risk of lung cancer in Chinese women who have never smoked. Indoor coal burning for heating and cooking in homes without adequate ventilation in China has also been implicated as a risk factor. Exposure to cooking oil vapours and indoor coal burning has been shown to be associated with an increased risk of lung cancer (Lam, 2005).

Policy options

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

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

Strategies for radon exposure avoidance may be divided into the following three principal categories:

1) Identification of houses with high radon levels and the remediation of these houses.

2) Reduction of the average indoor radon level in a country.

3) Coupling radon reduction strategies with national strategies aimed at reducing the consumption of cigarettes.

Chronic obstructive pulmonary disease (COPD)

Few studies investigated the association of non-smoking related COPD with indoor air exposure. Most of them assess the health effects of SHS exposure. SHS exposure may increase the frequency of respiratory symptoms in adults, and that these effects are estimated to be 30-60% higher in SHS exposed compared to unexposed nonsmokers. Significant relations between SHS exposure and COPD development have been found in the elderly, too, with an OR range of 1.68-5.63 (Jaakkola, 2002). The results of the reviewed epidemiological studies underline the relevance of preventative policy to reduce indoor environmental risk factors for respiratory diseases. For instance, as indicated by percentage of population attributable risk, the elimination of SHS exposure at home/work would abate the risk for COPD by about 12% (9% for chronic cough/phlegm) in Italian never-smoking women (Simoni et al., 2007). There is evidence that long-term exposure to mould/dampness is linked to higher risk for cough, phlegm, or dyspnoea, in adults (Alipour et al., 2006; de Hartog et al., 2003; Orozco-Levi et al., 2006; Simoni et al., 2007).

Policy options

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

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

Airborne respiratory infections

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

The most common routes of transmission are airborne, person to person or from a source, in particular from aquatic systems like air conditioning system, evaporative condensers, and humidifiers.

The infectious diseases include well-known infections like Legionnaire's disease (the incidence of Legionnaire's disease in Europe increased from 360 cases in 2000 to 864 cases in 2010 according to the European Legionnaires' Disease Surveillance Network (ELDSNet (De Jong et al., 2013), previously EWGLINET), tuberculosis and the flu, as well as new threats like Severe Acute Respiratory Syndrome (SARS). The symptoms of the airborne infectious diseases can be aggravated by exposure to SHS and combustion particles.

Policy options

1) To avoid overcrowded spaces if possible, especially in schools and health care facilities: The main source of infectious agents in the indoor environment are people. Therefore, it is difficult to regulate the main source and not possible to have any threshold limit. But indoor environment features play an important role in transmission of infectious agents – ventilation, air-conditioning, water or sewage ducts can transmit several infectious agents to rather long distances.

2) To guarantee the minimum air exchange rate in the buildings where people have to stay: The process of person- to- person transmission should be regulated especially in buildings where

children and young people gather, such as schools/kindergartens and day care facilities. For such buildings it is suitable to use the minimal air-exchange rate per person as a sort of regulation for infectious agent concentration. To achieve measured air exchange it is necessary to have either air condition systems or mechanical ventilation systems in all such buildings. Using natural ventilation is mostly a subjective measure and does not guarantee the required minimum air exchange – especially in cities where outdoor conditions may discourage from window opening.

3) To guarantee safe water and air (e.g. through limits for microbiological contamination): Secondary sources (water, dust) can play an important role even in other type of infections (alimentary – e.g. water-born cholera or some viruses causing alimentary problems). This transmission can also be regulated during the transmission process (limits of infection agents for drinking-water, air-condition systems without water stagnation, priority of cleaning procedures of air ducts especially in day care centres and facilities for children and young people). As to Legionellosis, prophylactic measures include regular cleaning and maintenance of different water systems.

Cardiovascular disease

Causes of cardiovascular disease (CVD) include:

Second-hand smoke (SHS) – Reviews summarizing the epidemiological studies about the association between SHS and increased risk of CVD concluded that the estimated risk for CVD related to SHS is about 25-30 (He et al., 1999).

Particles – Evidence is emerging that exposure to low concentration of PM is associated with cardiovascular mortality. Several studies have shown some link between outdoor PM and gas exposure and cardiovascular disease mortality and morbidity (Rich et al., 2005). Short-term effects of PM_{10} exposure include an increase in the overall cardiovascular mortality. Long-term exposure to $PM_{2.5}$ has been demonstrated to be independently related to cardiovascular mortality, in general, and in particular to mortality for ischemic heart disease, arrhythmia, heart failure, and cardiac arrest. Current evidence suggests a link between exposure to indoor PM and cardiovascular diseases onset, however, more research is needed. Further, there is a need to identify the role of the ultrafine particle fraction. Elevations in air pollution have also been associated with increased blood pressure.

Carbon monoxide – At CO levels typically encountered in indoor environments, health effects are most likely to occur in individuals who are physiologically stressed, either by exercise or by medical conditions that can make them more susceptible to low levels of CO. Subpopulations at increased risk of adverse effects include: individuals with cardiovascular diseases, pregnant women also with respect to fetal exposure, children, subjects with chronic obstructive pulmonary disease, individuals with reduced blood haemoglobin concentrations (Raub and Benignus, 2002). However, elevated CO levels can have various health effects, including cardiovascular effects and ischaemia, in both and healthy and susceptible individuals.

Gaseous pollutants – Epidemiological evidence of cardiovascular effects of NO_2 exposure proceeds from studies on outdoor air pollution. Moreover, it is very difficult to differentiate the effects of NO_2 from those of other pollutants in epidemiological studies. Literature about cardiovascular effects of SO_2 is poor, and it prevalently includes studies on outdoor air pollution health effects.

Policy options

PM – Exposure threshold levels are not yet specifically stated for indoor air. The American Society of Heating, Refrigerating, and Air-conditioning Engineers (ASHRAE) has adopted, for indoor air, the outdoor limits of the US-Environmental Protection Agency the National Ambient Air Quality Standards US-EPA-NAAQS), recommending a PM_{10} limit of 150 µg/m^3/24h.

This value is higher than the corresponding PM_{10} limit for outdoor air quality recommended by WHO (WHO Regional Office for Europe, 2006), that is 50 µg/m^3/24h and 20 µg/m^3/year. For outdoor $PM_{2.5}$ WHO suggests 25 µg/m^3/24h and 10 µg/m^3/year respectively. Although there are no indoor air guidelines for $PM_{2.5}$ and PM_{10}, WHO in its latest IAQ Guidelines (WHO Regional Office for Europe, 2010a) mentions that the guideline levels for ambient air are also applicable to indoor spaces.

Second-hand smoke (SHS) – The adverse effects of exposure to SHS are well established. SHS exposure occurs in private households, work, and public places. Several countries have enacted legislation that prohibits smoking in work and public places and schools, but the interest towards policies to address exposure in households is more limited.

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

Carbon monoxide – On the basis of human clinical data, a carboxyhaemoglobin (COHb) level of 2% should not be exceeded in human blood to protect susceptible population groups from acute exposure-related reduction of exercise tolerance and increase in symptoms of ischemic heart disease. In order not to exceed a COHb level of 2%, the following guideline values and periods of time-weighted average exposure have been determined by the WHO IAQ Guidelines (WHO Regional Office for Europe, 2010a):

- 100 mg/m^3 for 15 min
- 35 mg/m^3 for 1 hour
- 10 mg/m^3 for 8 hours
- 7 mg/m^3 for 24 hours

Regarding CO, the main measure to reduce CO levels is controlling the source of exposure. Management options include: connecting each combustion equipment/appliance to chimney or vented hood, ensuring sufficient local extract ventilation in kitchens with gas stove, mandatory inspection and maintenance of indoor combustion devices, and CO alarms.

Following policy options are also suggested:

- Restrict tobacco smoking in all indoor spaces;
- Restrict the construction of attached garages, or isolate them from living and working spaces;
- Ensure that ventilation dilutes predictable indoor emissions below the guideline levels;
- Raise public awareness about indoor air risks.

Gaseous pollutants – As to NO_2 in indoor air, a 1-hour guideline of 200 µg/m^3 is proposed, with an annual average not exceeding 40 µg/m^3 (WHO Regional Office for Europe, 2010a). Preventives measures to be adopted against NO_2 as well as NO include the control of the source, improvement of ventilation, and encouraged use of electrical kitchen appliances; use of unvented heating appliances should be avoided. As to ozone, the Air Quality Guidelines Global Update recommends a daily maximum 8-hour mean of 100 µg/m^3 in ambient air (WHO Regional Office for Europe, 2006).

List of acronyms

ALRI	Acute lower respiratory infections
BED	Biologically effective dose
BFR	Brominated flame retardants
BTEX	Benzene, toluene, ethylbenzene and xylenes
CFU	Colony-forming units
CI	Confidence interval
CO	Carbon monoxide
CO_2	Carbon dioxide
COHb	Carboxyhaemoglobin
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DALY	Disability-adjusted life years
EBD	Environmental burden of disease
EQLS	European Quality of Life Survey
ETS	see SHS
EU	European Union
EU-27	All 27 EU Member States as of 2012 (not including Croatia)
EU-15	EU Member States before 2004
EU-SILC	Statistics on Income and Living Conditions (Eurostat)
IAQ	Indoor air quality
IEQ	Indoor environmental quality
IgE	Immunoglobulin E
MVOC	Microbial volatile organic compounds
NMS-12	New EU Member States that joined the EU in 2004 and 2007 (not including Croatia)
NO	Nitric oxide or nitrogen oxide, also known as nitrogen monoxide
NO_x	Generic term for mono-nitrogen oxides NO and NO_2
NO_2	Nitrogen dioxide
O_3	Ozone
OR	Odds ratio
PB	Lead
PCB	Polychlorinated biphenyls
PAH	Polycyclic aromatic hydrocarbons
PBDE	Polybrominated diphenyl ethers
PM_{10}	Particulate matter with aerodynamic diameter of 10 micrometres or less
$PM_{2.5}$	Particulate matter with aerodynamic diameter of 2.5 micrometres or less
PM_1	Particulate matter with aerodynamic diameter of below 1 micrometer
S	Sulfur
SES	Socioeconomic status
SBS	Sick building syndrome
SHS	Second-hand smoke (often referred to as ETS – environmental tobacco smoke)
SO_2	Sulfur dioxide
TVOC	Total volatile organic compounds
UFP	Ultrafine particles (less than 100 nanometres in diameter)
VOC	Volatile organic compounds
WHO	World Health Organization

Millions of citizens within the WHO European Region spend approximately 90% of their time indoors: in their homes (2/3 of this time), workplaces, schools, and public spaces. Despite undeniable improvements in the quality of indoor environments in the last twenty years, a range of health risks still exists, such as indoor air pollution, injury risks, noise, humidity, mould growth, inadequate indoor temperature, lack of hygiene and sanitation equipment, and crowding. Many of these risks are either directly or indirectly related to the quality of the building. Furthermore, problems with building quality disproportionally affect vulnerable population groups in terms of socioeconomic status or class age.

Despite the scientific progress in understanding the connection between indoor environments and health, evidence is often restricted to categorical studies targeting specific health risks and/or outcomes; much less evidence is available regarding the combined or multiple exposure to risk factors.

This report aims to explore and shed light on the links between different exposure stressors and modifiers people confront in residential dwellings, day care centers, schools and kindergartens. It summarizes a systematic review of literature and project reports presenting evidence on multiple or combined risk exposure in indoor environments, covering the range of health risks encountered.

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